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# <Review Article>Enzymic Dehydrogenation of p-Coumaryl Alcohol and Syntheses of Oligolignols

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CITATION:

NAKATSUBO, Fumiaki. <Review Article>Enzymic Dehydrogenation of p-Coumaryl Alcohol and Syntheses of Oligolignols. Wood research : bulletin of the Wood Research Institute Kyoto University 1981, 67: 59-118

ISSUE DATE:

1981-03-30

URL:

<http://hdl.handle.net/2433/53353>

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# Enzymic Dehydrogenation of *p*-Coumaryl Alcohol and Syntheses of Oligolignols

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## Introduction

Lignin, one of the most important constitutional components of vascular plants, comprises about 20–30% of woods and 15–20% of grasses in dry weight<sup>1)</sup> and its abundance is the second of natural organic materials to cellulose on the earth. Lignin is being important economically related to the recent serious problem driven from the shortage of fossilized resources. Lignin, which widely occurs in vascular plants above the pteridophyte level<sup>2)</sup>, functions as a binding and encrusting materials for cell walls composed of cellulose and hemicelluloses giving rigidity to the wall in order to resist

\* Research Section of Lignin Chemistry

rigorous external conditions such as gravity, wind, rain and attack of wood-decay fungi. It is also considered that lignin protects water leaking from the cell walls by lining cell walls of the conductive tissue in which water is transported smoothly from root to metabolic tissues, such as leaves, flowers, etc.

The difficulty of elucidating the chemical structure of lignin over one hundred years since the term "Lignin" was proposed by F. Schulze in 1857<sup>3)</sup> should be ascribed to its complexity; lignin has neither regularity, optical activity nor crystallinity which has made it impossible to determine by X-ray analysis unlike other natural polymers such as cellulose, protein, DNA, RNA etc. Therefore, it is inevitable fate that lignin structure is described only as a statistical combination pattern of probable substructures and not as definite one. However, current knowledge of lignin structure which has been obtained as the result of continuous investigations by a great number of researchers over one hundred years, is probably close to the truth, qualitatively and quantitatively<sup>4)</sup>.

The history of the structural studies of lignin seems to be divided into three periods: The first is the period of about sixty years from the proposal of "encrusting material" by Payen in 1838<sup>5)</sup> to the "Coniferyl alcohol theory" by Klason in 1897<sup>6)</sup>. At the end of this period, Klason proposed the idea that lignin is chemically related to coniferyl alcohol which might be linked together by a continuous condensation between alcoholic and phenolic hydroxyl groups. Although he could not solve the problem "how is coniferyl alcohol linked to each other", his basic idea on coniferyl alcohol undoubtedly greatly influenced the thinking of later lignin chemists.

We had to wait for the solution of the problem fifty years, the second period when the "Dehydrogenation theory" that lignin is formed by dehydrogenation of phenolic  $\alpha,\beta$ -unsaturated  $C_6C_3$  progenitors of the coniferyl alcohol type was proposed by H. Erdtman in 1933<sup>7,8)</sup> and K. Freudenberg in 1942<sup>9)</sup>.

The third period of lignin research history is about forty years from 1942 to today and during this period experimental results justifying the dehydrogenation theory have been obtained. The validity of the dehydrogenation theory has been sufficiently established through the enzymic dehydrogenation experiments of *p*-hydroxycinnamyl alcohols, the structural determination of the products obtained by the various degradation methods, spectral and functional analysis of lignins, and structural simulation of lignin by computer<sup>10)</sup>; the structures of softwood-<sup>4)</sup> and hardwood lignins<sup>11)</sup> can be illustrated.

On the other hand, in the history of lignin studies the chemistry of pulping can not be neglected. In 1874, the sulfite pulping method was first industrialized by E. Ekman in Sweden. This remarkably stimulated the structural studies of lignin and the lignin study from pulping aspect started with softwood lignin because only softwood was used at that time for pulping. With the exhausting of softwoods, hard-

woods and grasses had to be used for pulping and the lignin studies were shifted to hardwood and grass lignins from softwood lignin. Now, lignins can be divided into three groups, softwood, hardwood and grass lignins by the plant sources.

Softwood (gymnosperm) lignin is a dehydrogenation polymer of coniferyl alcohol. Hardwood (angiosperm) lignin is a mixed dehydrogenation polymer of coniferyl and sinapyl alcohols and grass lignin is composed of a mixed dehydrogenation polymer of coniferyl, sinapyl and *p*-coumaryl alcohols, and in grass lignin, 5–10% of *p*-coumaric acid is esterified to the C $\gamma$ -hydroxyl groups of the side chains in the lignin polymer<sup>12)</sup>.

It is considered that enzymic dehydrogenation studies are basic and most important to elucidate the structures of lignins, and this has been established by the dehydrogenation studies of *p*-hydroxycinnamyl alcohols. The dehydrogenation of coniferyl and sinapyl alcohols by mushroom laccase was first carried out by K. Freudenberg<sup>13)</sup>.

The dehydrogenation of *p*-coumaryl alcohol discussed in this paper has been studied in comparison with that of coniferyl alcohol by K. Freudenberg<sup>14)</sup>. The elementary analysis and hydrogen absorption analysis by the formed DHP (dehydrogenation polymer) of *p*-coumaryl alcohol showed that this DHP is similar to that from coniferyl alcohol. *p*-Coumaryl alcohol having no methoxyl groups at the *ortho*-position of phenolic group has a possibility to react preferentially at this positions to give a much more condensed type, "double condensation" proposed by D. E. Bland<sup>15)</sup>. Recently Yamasaki *et al.*<sup>16)</sup> found the same condensation pattern as in coniferyl alcohol DHP found by K. Freudenberg from the various degradation studies of the *p*-coumaryl alcohol DHPs. However, the dehydrogenation studies of *p*-coumaryl alcohol studied so far is only concerned with DHP polymer and not with dimer formation.

In Section 1-1, the isolation and the structural determination of the dimeric compounds of *p*-coumaryl alcohol obtained by the dehydrogenation are described. In Section 1-2, the formation mechanism and the stereochemistry of the arylglycerols which have been isolated from the degradation products of natural lignins are investigated in connection with the dehydrogenation of *p*-coumaryl alcohol. The stereochemistry of the phenylcoumaran substructures, dehydrodiconiferyl alcohol and dehydrodi-*p*-coumaryl alcohol, and the analysis of dimeric compounds described in Section 1-1 by gas chromatography and NMR spectrometry are discussed in Section 1-3 and 1-4, respectively, compared with those of coniferyl alcohol. The *threo* isomers of *p*-hydroxyphenylglycerol- $\beta$ -*p*-coumaryl ether and arylglycerols obtained in the investigations described in Section 1-1 and 1-2, respectively, were found to predominate over *erythro* isomers. This *erythro*/*threo* determining step, the water addition step to quinonemethide which is an important intermediate after radical formation, and subsequent coupling step involved in lignin polymerization is discussed in Section 1-5.

The isolation and structural identification of the products in the dehydrogenation and lignin degradation have been the most important works in the structural studies of lignin. It is generally considered in the chemistry of natural products that the final proof of the structure of compounds are obtained by the syntheses. In lignin chemistry the structures have been scarcely proved by syntheses because, unfortunately, the general synthetic method for these oligomers has not yet been established. The general synthetic method for the oligolignols, involving  $\beta$ -hydroxy ester intermediates, focused on the common unit of lignin substructures, *p*-oxyphenylpropane-1,3-dioxy structure, is described in Section 2.

The arylglycerol- $\beta$ -aryl ether substructure is the most important interphenylpropane unit in lignins: 30–50% or more of the phenylpropane units are found to occur as this substructure in lignin. For this reason, guaiacylglycerol- $\beta$ -guaiacyl ether has been generally used as a lignin model compound. In Section 2-1, a new method by a convergent synthesis of the compound is described. The convergent synthetic method involving  $\beta$ -hydroxy ester intermediate established in Section 2-1 was further applied to the synthesis of guaiacylglycerol- $\beta$ -coniferyl and  $\beta$ -coniferyl aldehyde ethers in Section 2-2. 1,2-Diarylpropane-1,3-diol substructure is also quite common in lignins and its general synthetic method involving  $\beta$ -hydroxy ester intermediate is discussed in Section 2-3. In Section 2-4, the general synthetic method of phenylcoumaran whose synthesis has not been reported, is described. Finally, in Sections 2-5 and 2-6, the application of the general synthetic method established in the preceding Sections to the syntheses of the trilignols composed of phenylcoumaran,  $\beta$ -O-4 and  $\beta$ -1 substructures is described.

## 1. Enzymic dehydrogenation of *p*-coumaryl alcohol

### 1.1 Structures of dimeric compounds<sup>17)</sup>

It is believed that the grass lignin is a polymer composed of *p*-hydroxyphenyl, guaiacyl and syringyl propane units and is characterized by the occurrence of a larger amount of *p*-hydroxyphenyl unit than in hard- and soft-wood lignins<sup>18)</sup>. Although some of *p*-hydroxyphenyl unit (about 10%) have been ascribed to the esterified *p*-coumaric acid<sup>12)</sup>, major portions of the unit should be due to the lignin polymer. Thus, elucidation of enzymic dehydrogenation of *p*-coumaryl alcohol (1) may conceivably provide useful informations on the chemical structure of *p*-hydroxyphenyl component of the grass lignin.

In this Section, the chemical structures of the four dimeric compounds, *p*-coumarylresinol (2), dehydrodi-*p*-coumaryl alcohol (3), *p*-hydroxyphenylglycerol- $\beta$ -*p*-coumaryl ether (4) and 2-(4-hydroxyphenyl)-3-hydroxymethyl-4-( $\alpha$ ,4-dihydroxybenzyl)-tetrahydrofuran (monoepoxylignan) (5) obtained by enzymic dehydrogena-

tion of *p*-coumaryl alcohol are described.

### 1.1.2 Isolation and identification of dimeric compounds

A flow sheet of the dehydrogenation procedure of *p*-coumaryl alcohol is shown in Fig. 1. The ethyl acetate soluble portion was applied onto silica gel column chromatography and the column was eluted with a mixture of benzene and ethyl acetate. *p*-Coumarylresinol (2), dehydrodi-*p*-coumaryl alcohol (3), *p*-hydroxyphenylglycerol- $\beta$ -*p*-coumaryl ether (4) and monoepoxy lignan (5) were obtained respectively. The compounds (2–4) correspond to the three dimeric compounds obtained in the dehydrogenation of coniferyl alcohol by Freudenberg *et al.*<sup>19)</sup> However, the compound (5) is a new dimer whose formation is interesting in view of coupling mechanism of the phenoxy radical of *p*-coumaryl alcohol as described later.

The NMR spectrum of *p*-coumarylresinol diacetate is shown in Fig. 2. The

*p*-Coumaryl alcohol (10 g) in H<sub>2</sub>O (1200 ml), 0.1% H<sub>2</sub>O<sub>2</sub> (1700 ml),  
Phosphate buffer, Peroxidase (20 mg) Stirred for 3.5 hrs.

Filtered  
 |  
 Filtrate ————— DHP (3.15 g)  
 |  
 Extracted with EtOAc (500 × 5, 250 × 3 ml)  
 |  
 EtOAc layer, dried over Na<sub>2</sub>SO<sub>4</sub>  
 |  
 Evaporated  
 |  
 Residue (7.17 g)  
 |  
 Applied onto Silica Gel Column (5 × 120 cm, 700 g)  
 |  
 Eluted with benzene/EtOAc  
 |  
 Isolated (2), (3), (4) and (5)

Fig. 1. Isolation of dimeric from the dehydrogenation products of *p*-coumaryl alcohol.

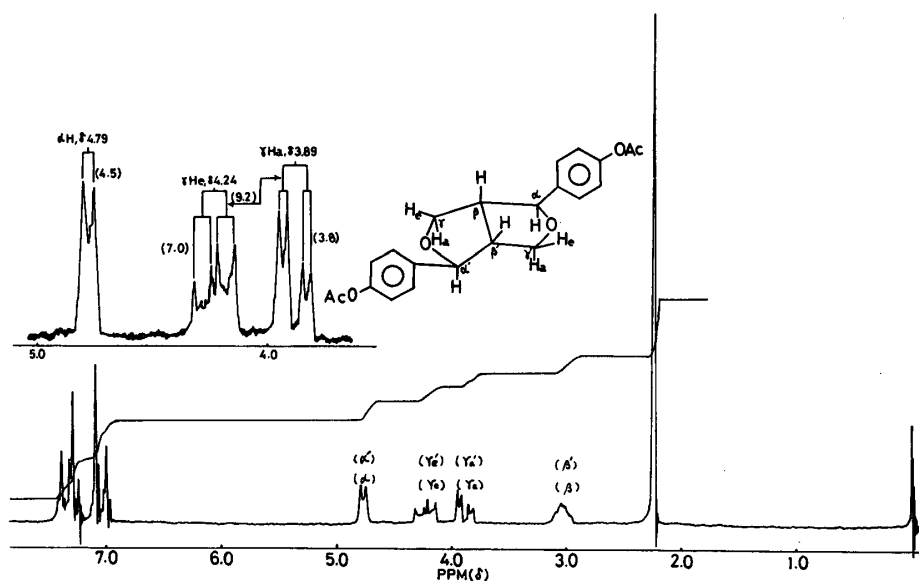


Fig. 2. NMR spectrum of *p*-coumarylresinol diacetate.

chemical shifts and the coupling modes of the protons attached to the tetrahydrofuran ring are approximately identical to those of the rings of pinoresinol<sup>20)</sup>, sesamine<sup>21)</sup> and syringaresinol<sup>22)</sup>. The results indicate that the chemical shifts and the coupling modes of the protons attached to the tetrahydrofuran rings are hardly influenced by the substituent groups on the aromatic rings. The signals of the equatorial protons on the carbons give a quartet at  $\delta 4.24$  whose coupling constants are  $J_{\text{He},\beta\text{H}}=7.0$  and  $J_{\text{He},\text{Ha}}=9.2$ , whereas axial protons give a quartet at  $\delta 3.89$  as well, and the coupling constants are  $J_{\text{Ha},\beta\text{H}}=3.8$  and  $J_{\text{Ha},\text{He}}=9.2$ , respectively. On the other hand, the protons of He and He' are of *cis* configuration and the Ha and Ha' are *trans* to the adjacent  $\beta$ - and  $\beta'$ -protons, respectively. In conclusion, the protons with *cis* configuration on the tetrahydrofuran ring give larger coupling constants than those with *trans* configuration. This fact gives information for the possible configuration of monoepoxylignan (5) as explained later.

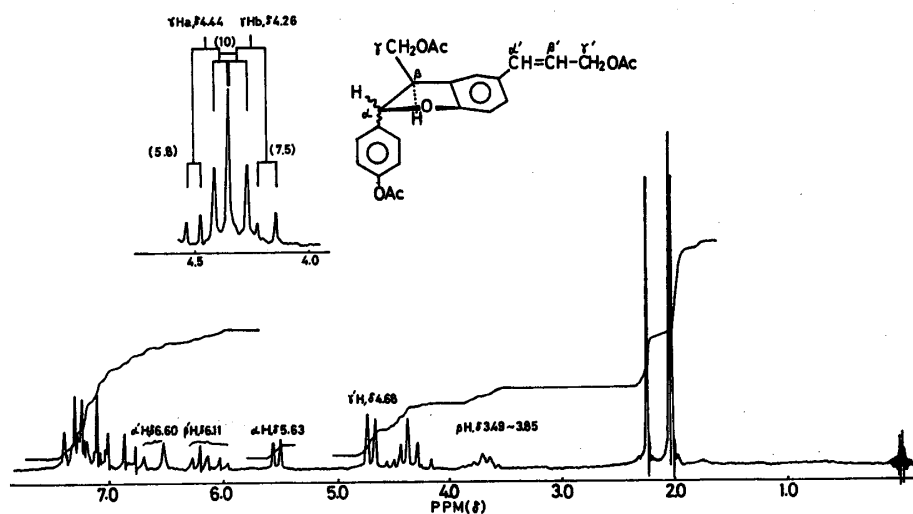


Fig. 3. NMR spectrum of dehydrodi-*p*-coumaryl alcohol triacetate.

The NMR spectrum of dehydrodi-*p*-coumaryl alcohol triacetate, corresponded to that of dehydrodiconiferyl alcohol, is shown in Fig. 3. Each  $\gamma$ -CH<sub>2</sub> proton gives a quartet because of their nonequivalency. Designating the two protons as Ha and Hb tentatively as given in Fig. 3, the Ha gives a quartet at  $\delta 4.44$  having  $J_{\text{Ha},\text{Hb}}=10$  and  $J_{\text{Ha},\beta\text{H}}=5.8$ , respectively, and the Hb gives a quartet as well at  $\delta 4.26$  having  $J_{\text{Ha},\text{Hb}}=10$  and  $J_{\text{Hb},\beta\text{H}}=7.5$ , respectively. It is understandable that the nonequivalency is probably due to  $\beta$ -asymmetric carbon and not to the inhibition for the rotation of C $\beta$ -C $\gamma$  bond as described by Ludwig *et al.*<sup>23)</sup> This is supported by the fact that the  $\gamma$ -CH<sub>2</sub> protons of *p*-hydroxyphenylglycerol- $\beta$ -*p*-coumaryl ether (4) which has no such effect for the C $\beta$ -C $\gamma$  bond give quartets as well. For the protons attached to C $\beta$  and C $\gamma$  of the coumaran ring, Ludwig *et al.*<sup>23)</sup> proposed *trans* configuration based only on the fact that the configuration of C $\beta$  and C $\gamma$  protons of de-

hydrodiisoeugenol was *trans*. However, in the NMR spectrum of dehydrodiisoeugenol (synthesized by the method of B. Leopold<sup>24</sup>) and its NMR spectrum was measured using the same instrument in our laboratory), the proton of  $\alpha$ -CH gave a doublet at  $\delta$ 5.12 ( $J=9.0$ ) which was markedly different from those of the former two coumarans as respect to the chemical shifts and coupling constants. Consequently, it is doubtful from the NMR spectra whether these coumarans have the same configuration, although *trans* configuration is conceivable from the reaction mechanism. The conclusive evidence for the *trans* configuration of dehydrodi-*p*-coumaryl alcohol (3) and dehydrodiconiferyl alcohol is presented in Section 1-3.

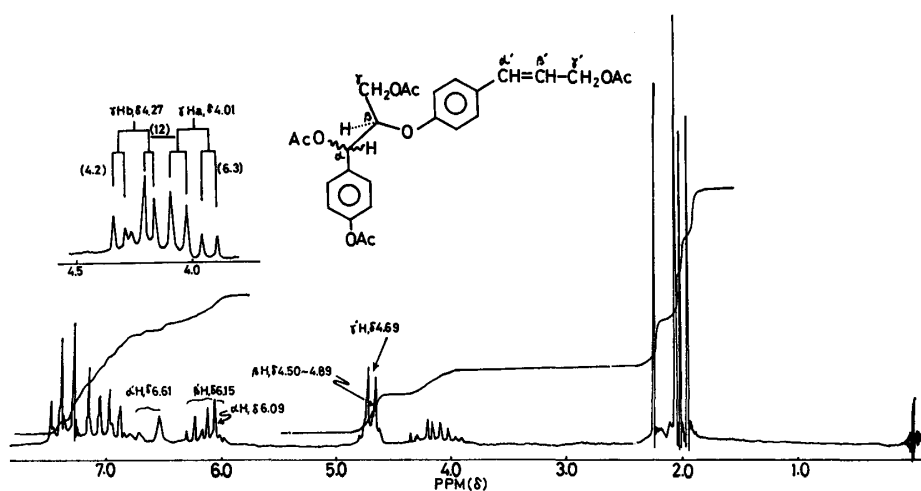


Fig. 4. NMR spectrum of *p*-hydroxyphenylglycerol- $\beta$ -*p*-coumaryl ether tetraacetate.

*p*-Hydroxyphenylglycerol- $\beta$ -*p*-coumaryl ether (4) was isolated as a mixture of *threo* and *erythro* isomers which did not crystallize. The NMR spectrum of the acetate is shown in Fig. 4. The NMR spectrum suggests that the mixture consists mainly of the *threo* isomer indicating a relatively clear doublet peak of the  $\alpha$ -CH proton. The nonequivalency of the  $\gamma$ -protons is more remarkable than in the case of coumaran. Designating the two protons as Ha and Hb as in the case of coumaran, the Ha gives a quartet at  $\delta$ 4.01 having  $J_{Ha,Hb}=12$  and  $J_{Ha,\beta H}=6.3$  and the Hb gives a quartet as well at  $\delta$ 4.27 having  $J_{Ha,Hb}=12$  and  $J_{Hb,\beta H}=4.2$ , respectively.

The NMR spectrum of monoepoxylignan tetraacetate whose signals are assigned by the decoupling method is shown in Fig. 5. A doublet peak at  $\delta$ 5.73 is assigned to  $\alpha$ -methine proton which shifts from  $\delta$ 4.95 by acetylation. On the other hand, a doublet peak at  $\delta$ 4.55 is assigned to  $\alpha'$ -methine proton attached to the ether bond because of the retention of original chemical shift after acetylation. Irradiation of the peaks corresponding to  $\beta$ -proton ( $\delta$ 2.45–2.85) and  $\beta'$ -proton ( $\delta$ 1.80–2.20) caused two doublet peaks at  $\delta$ 5.73 and  $\delta$ 4.55 to collapse to respective broad singlets, and the peaks of  $\gamma$ -CH<sub>2</sub> protons at  $\delta$ 3.80–4.20 to broad peaks. The results indicate the existence



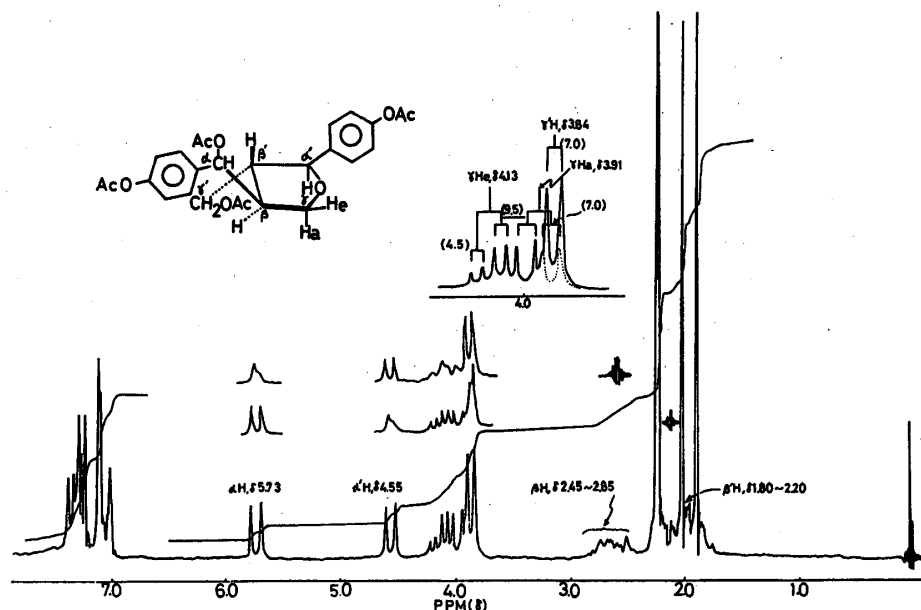
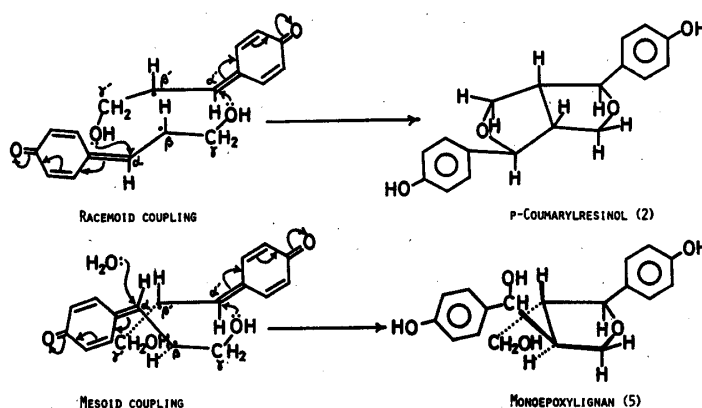


Fig. 5. NMR spectrum of monoepoxylignan tetraacetate.

of spin-spin coupling between them, and these NMR data give information concerning the structure of the compound (5). The configuration of  $C\beta$  and  $C\beta'$  is assumed to be *trans* which differs from resinol (2) by the following facts. The He on the tetrahydrofuran ring gives a quartet having  $J_{He, Ha}=9.5$  and  $J_{He, \beta H}=4.5$ , and Ha gives also the same pattern having  $J_{Ha, He}=9.5$  and  $J_{Ha, \beta H}=7.0$ , respectively. That is,  $J_{Ha, \beta H}(7.0)$  is larger than  $J_{He, \beta H}(4.5)$ . Consequently, the Ha is *cis* relative to  $\beta H$  and He is *trans* to  $\beta H$ , respectively. If this interpretation is correct, the configuration of  $C\beta$  and  $C\beta'$  must be *trans*.

Fig. 6. Formation mechanism of *p*-coumarylresinol (2) and monoepoxylignan (5).

This conclusion is supported by the reaction mechanism in formation of (5). At the  $C\beta$  and  $C\beta'$  coupling in dehydrogenation of *p*-hydroxycinnamyl alcohols, two

modes, *racemoid* and *mesoid* types are probable as shown in Fig. 6. In *racemoid* coupling, when one quinonemethide is attacked by the hydroxyl group attached to the C $\gamma$  to form a tetrahydrofuran ring, the other quinonemethide and the  $\gamma'$ -hydroxyl group is favorably located for ring closure so that the ring closure proceeds smoothly to produce resinol (2). On the other hand, in *mesoid* coupling, when ring closure of one tetrahydrofuran proceeds, the other quinonemethide is no longer located to be attacked by the  $\gamma'$ -hydroxyl group because of the *trans* configuration of C $\beta$  and C $\beta'$ . Consequently, quinonemethide is attacked by water in medium to produce monoepoxylignan (5). Thus, the monoepoxylignan which was first isolated in the present investigation seemed to be produced by the *mesoid* type coupling.

Recently, Sarkanen *et al.*<sup>25)</sup> described that the *racemoid*  $\beta$ - $\beta'$  coupling mode appears to be exclusive for *trans* isomer, while both *racemoid* and *mesoid*  $\beta$ - $\beta'$  couplings occur in *cis* isomer. Thus, it may be assumed that the monoepoxylignan (5) is produced by the *mesoid* coupling mode of a trace amount of *cis* *p*-coumaryl alcohol contaminated in *trans* isomer. But, the monoepoxylignan (5) was also identified in the dehydrogenation products by gas chromatography even when the contaminated *cis* isomer was completely removed by recrystallization of the *trans* *p*-coumaryl alcohol. Therefore, the monoepoxylignan (5) obtained in the present investigation was formed from *trans* *p*-coumaryl alcohol. The ratio of the two coupling modes is described in Section 1-4.

## 1.2 Enzymic formation of arylglycerols from *p*-hydroxycinnamyl alcohols<sup>26)</sup>

Since the finding of guaiacyl- and syringylglycerols in the mild hydrolysis products of conifer- and hardwood lignins<sup>27,28)</sup>, the origin of both compounds has been ascribed to hydrolysis of arylglycerol moiety of guaiacyl- and syringylglycerol- $\beta$ -arylpropane ether units, respectively, and the occurrence of free arylglycerol side chains in lignin molecules has been doubted.

However, guaiacylglycerol was recently isolated from the degradation products of spruce lignin with sodium in liquid ammonia<sup>29,30)</sup>, and the occurrence of arylglycerol unit itself has been suggested. The present investigation describes the formation and possible incorporation of arylglycerols into dehydrogenation polymers in enzymic dehydrogenation of *p*-hydroxycinnamyl alcohols as lignin precursor.

### 1.2.1 Isolation and identification of arylglycerols

A flow sheet of separation procedures for the dehydrogenation products of *p*-hydroxycinnamyl alcohols by peroxidase/H<sub>2</sub>O<sub>2</sub> and fungal laccase/O<sub>2</sub> is shown in Fig. 7.

All dimers expected from the oxidative couplings of the respective *p*-hydroxycinnamyl alcohols were isolated from the ethyl acetate soluble fractions of the dehydrogenation products and identified. Furthermore, guaiacylglycerol, syringylglycerol

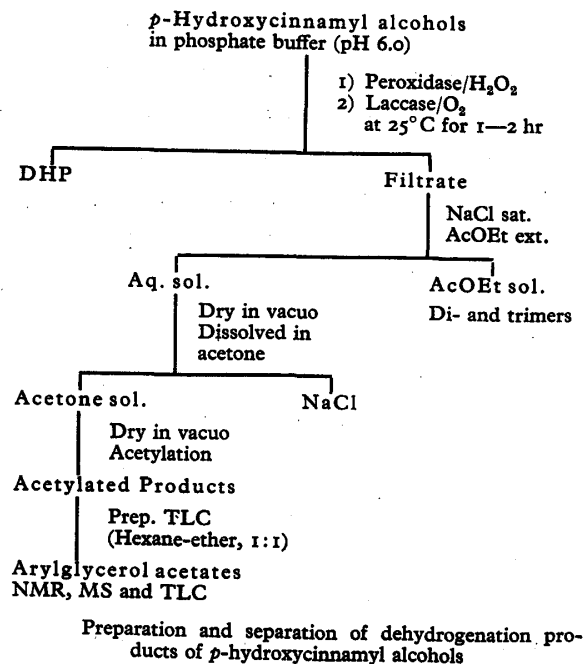


Fig. 7

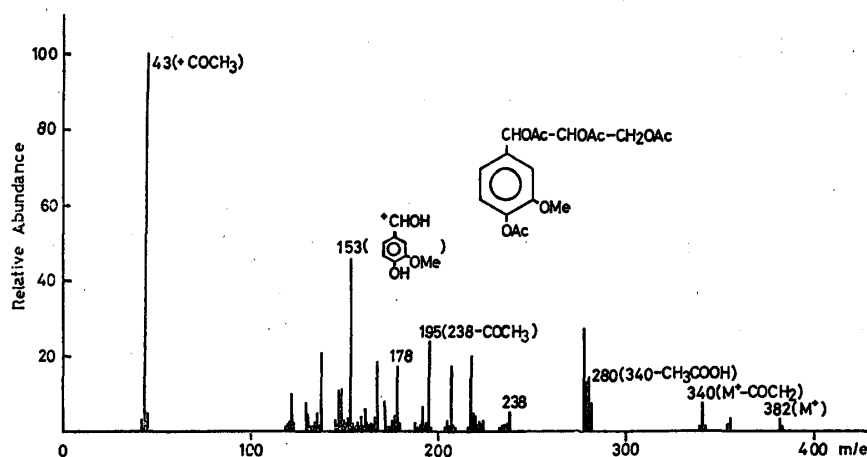


Fig. 8. Mass spectrum of guaiacylglycerol tetraacetate.

and *p*-hydroxyphenylglycerol which have not been reported in the dehydrogenation products of the corresponding *p*-hydroxycinnamyl alcohols were isolated for the first time from the water soluble and ethyl acetate insoluble fractions of the dehydrogenation products and identified by GC-MS and NMR spectrometries. The mass spectra of guaiacyl-, syringyl- and *p*-hydroxyphenylglycerol tetraacetates are shown in Fig. 8, 9 and 10. These arylglycerols were obtained as a mixture of *threo* and *erythro* isomers which were separated by glc (Fig. 11, 12 and 13). Table 1 shows the ratio of both isomers estimated from the peak area on the gas chromatograms. The amounts of *threo* isomers were 1–4 times higher than those of *erythro* isomers, and the results, especially the case of guaiacylglycerol, were in good agreement with the results from

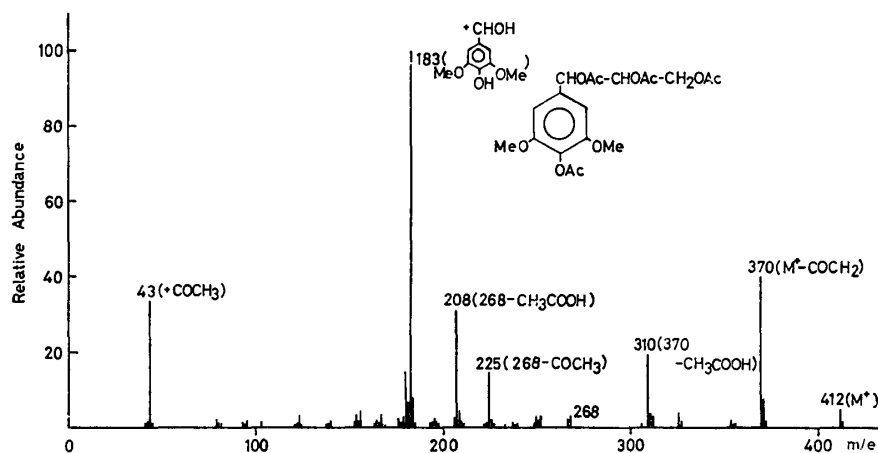
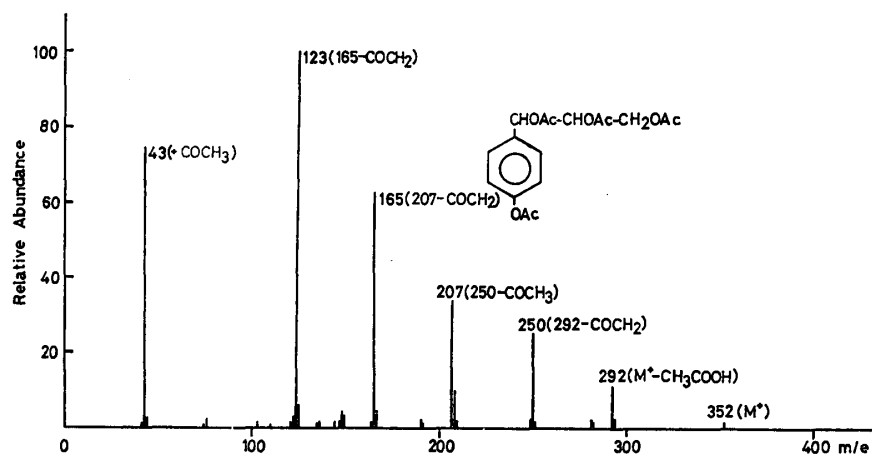


Fig. 9. Mass spectrum of syringylglycerol tetraacetate.

Fig. 10. Mass spectrum of *p*-hydroxyphenylglycerol tetraacetate.

the hydrolysis and sodium-liquid ammonia degradation of lignin<sup>29,30</sup>. The yields of arylglycerols obtained by the mediation of both enzymes are shown in Table 2, and 0.03%–0.6% of *p*-hydroxycinnamyl alcohols were found to be converted to the corresponding arylglycerols.

Nimz<sup>27,28</sup> has isolated and identified guaiacylglycerol, guaiacylglycerol- $\beta$ -guaiacylglycerol ether and syringylglycerol by hydrolysis of finely-powdered spruce and beech woods with percolating water at 100°C. Subsequently Omori and Sakakibara<sup>31</sup> further isolated syringylglycerol- $\beta$ -syringylglycerol ether as well as guaiacyl- and syringylglycerols from the hydrolysis products of *Fraxinus* wood meal.

The formation of these arylglycerol compounds in hydrolysis has been explained by direct nucleophilic displacement of the  $\beta$ -ether moiety of arylglycerol- $\beta$ -ether units in lignin molecules under mildly acidic conditions<sup>32</sup>. However, the mild hydrolysis of guaiacylglycerol- $\beta$ -guaiacyl ether did not give any guaiacylglycerol, whereas moderately strong acid hydrolysis gave exclusively Hibbert's ketones<sup>33</sup>. Yamaguchi<sup>29</sup>

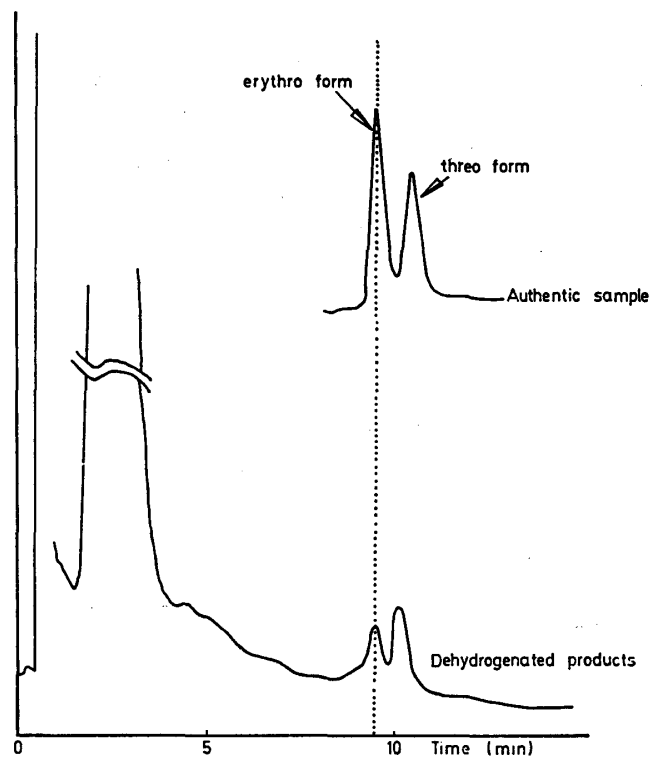


Fig. 11. Gas chromatogram of guaiacylglycerol tetraacetate.  
2% OV-17 on Chromosorb AW, 2m, 218°C.

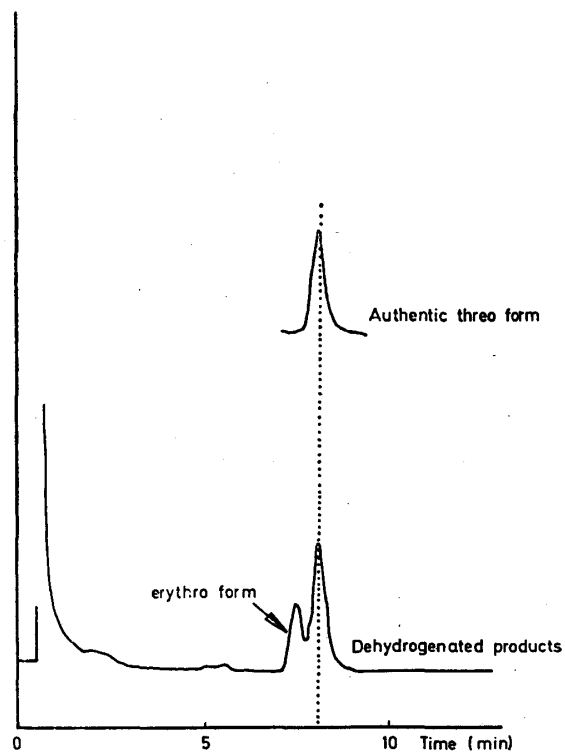


Fig. 12. Gas chromatogram of syringylglycerol tetraacetate 2% OV-17  
on Chromosorb AW, 2m, 240°C.

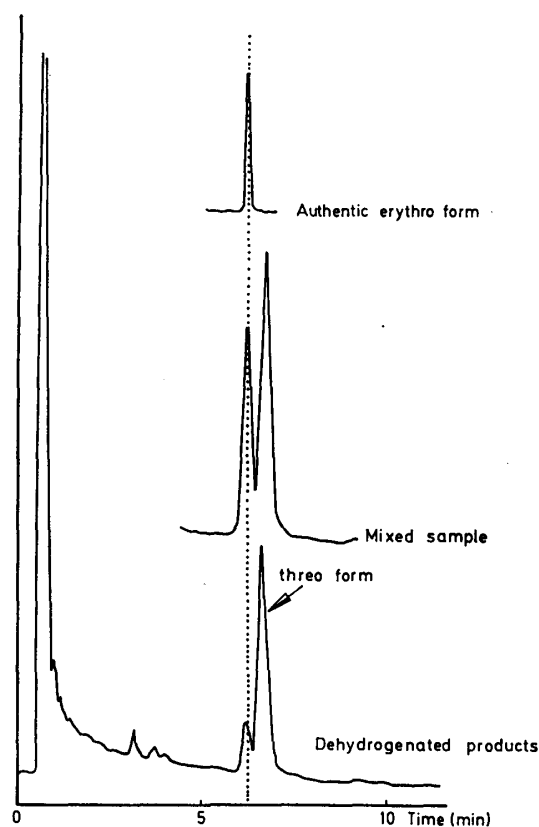


Fig. 13. Gas chromatogram of *p*-hydroxyphenylglycerol tetraacetate 2% OV-17 on Chromosorb AW, 2 m, 218°C.

Table 1. Ratio of peak area of *erythro*- and *threo* isomers of arylglycerol tetraacetates.

Compound	<i>erythro</i> %	<i>threo</i> %
Guaiacylglycerol tetraacetate	45	55
Syringylglycerol tetraacetate	26	74
<i>p</i> -Hydroxyphenylglycerol tetraacetate	19	81

Table 2  
Yields of dehydrogenation products of *p*-hydroxycinnamyl alcohols

Substrate	DHP %	Ethylacetate sol. %	Water sol. %	Arylglycerol acetate	
				mg	% ***
Coniferyl 1)* . . . . .	66.1	36.9	1.5	6.0	0.06
alcohol 2)** . . . . .	60.3	41.9	2.8	13.0	0.20
Sinapyl 1) . . . . .	10.7	79.6	14.0	9.6	0.60
alcohol 2) . . . . .	13.6	81.1	6.3	8.0	0.50
<i>p</i> -Coumaryl 1) . . . . .	30.0	70.0	1.2	5.0	0.03
alcohol 2)**** . . . . .	4.3	108.9	0.6	3.4	0.20

\*1) peroxidase/H<sub>2</sub>O<sub>2</sub>, \*\*2) laccase/O<sub>2</sub>, \*\*\* value as acetyl-free arylglycerol, \*\*\*\* laccase of low activity was used

found that guaiacylglycerol, in the degradation of spruce lignin with sodium in liquid ammonia, is not derived from guaiacylglycerol- $\beta$ -aryl ether units.

Considering these results and the present investigation it is concluded that the arylglycerols obtained as degradation products of lignins can be ascribed to arylglycerol units which were formed by the coupling of  $\beta$ -radicals of *p*-hydroxycinnamyl alcohols with phenoxy radicals of arylglycerols during enzymic dehydrogenation, and that lignins contain arylglycerol units with free glycerol side chain as original structure.

In the present investigation only arylglycerols which are very soluble in water were estimated. Since a considerable portion of the arylglycerol is supposed to be incorporated into arylglycerol- $\beta$ -aryl glycerol ether substructures in polymers during dehydrogenation, the total amount of the arylglycerols formed should be higher than those estimated.

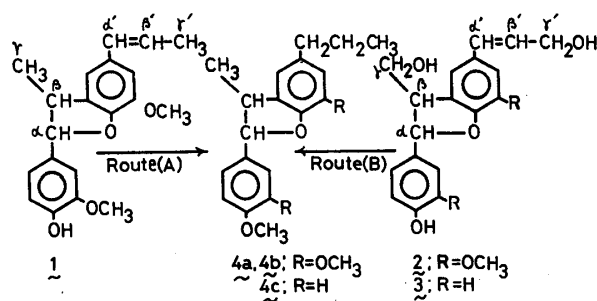
### 1.3 Configuration of phenylcoumarans<sup>34)</sup>

In Section 1-1, isolation and identification of the four dimers obtained by dehydrogenation of *p*-coumaryl alcohol were described. But the configuration of the coumaran ring of dehydrodi-*p*-coumaryl alcohol (3) has remained unknown.

In the present Section, the *trans* configuration of the coumaran portions of both dehydrodiconiferyl alcohol (2) and dehydrodi-*p*-coumaryl alcohol (3) is discussed.

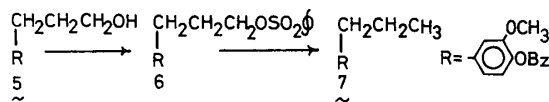
#### 1.3.1 Configuration of dehydrodiconiferyl alcohol

G.A. Erdtman *et al.*<sup>35)</sup> determined that the configuration of the coumaran portion of dehydrodiisoeugenol (1) is *trans* on the fact that the compound gave *erythro*- $\beta$ -methyl malic acid after treating with ozone in acetic acid. The configuration of dehydrodiconiferyl alcohol (2) is considered to be determined by comparing the spectral property of (1) to that of (2) after the  $\gamma,\gamma'$ -hydroxymethyl groups of the latter are reduced to the methyl groups.

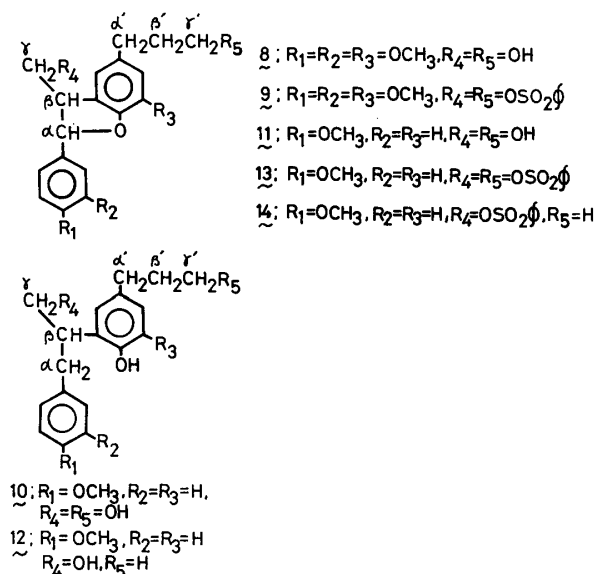


Thus, comparison of the two coumarans (4a) and (4b) which are synthesized through both (A) and (B) routes should make it possible to determine the configuration of (2). The model experiment was then carried out for reduction of the  $\gamma,\gamma'$ -hydroxymethyl groups to methyl groups. Dihydroconiferyl alcohol benzyl ether (5) used as a model compound was synthesized in almost quantitative yield from eugenol by

benzylation and subsequent hydroboration. The compound (5) was sulfonated with benzene sulfonyl chloride in pyridine and the sulfonate (6) was reduced with lithium aluminum hydride to the expected compound (7) in 85% overall yield. Thus, the



hydroxymethyl groups were reduced to methyl groups, and the synthesis of (4b) was undertaken. First, the compound (4a) was synthesized through the route (A) by methylation of (1) with diazomethane followed by catalytic hydrogenation with Pd-carbon in methanol, and the product was crystallized from methanol. Alternatively, the compound (4b) was synthesized through the route (B) according to the same method as in the case of model compound (5). That is, the compound (2)



was reduced with Pd-carbon in methanol and the dihydro compound thus obtained was methylated with diazomethane to the compound (8). On the NMR spectrum of (8), both the chemical shift and coupling constant of  $\alpha$ -methine proton were almost the same as those of the compound (2) suggesting that the chemical shift of  $\alpha$ -methine proton was little affected by the substituent groups of the aromatic rings. Since the configuration of the coumaran portion seems to be unchanged during reaction steps, the compound (8) must hold the same configuration as (2). The compound (8) was sulfonated with benzene sulfonyl chloride in pyridine at 5°C and the sulfonate (9) obtained was immediately reduced with lithium aluminum hydride without crystallization. After reduction for 30 min. at room temperature, the product (4b) was extracted with ether, purified by preparative tlc and crystallized from methanol.



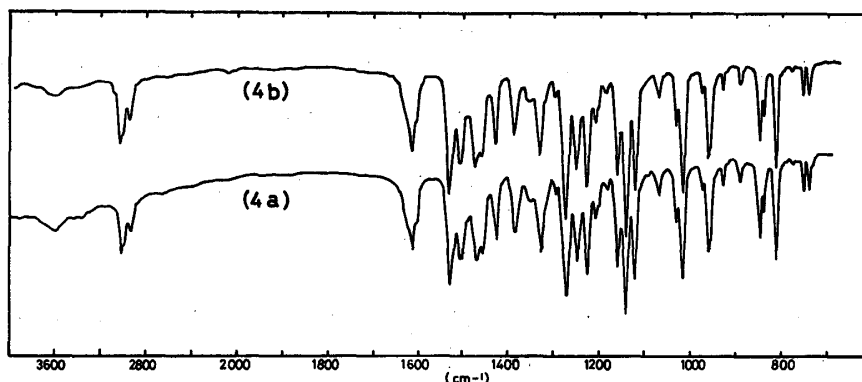


Fig. 14. IR spectra of 4a and 4b.

It was concluded that these two coumarans (4a) and (4b) synthesized through both (A) and (B) routes, were identical by the following facts. 1) The mixed melting point showed no depression. 2) All the spectral data of NMR, IR (Fig. 14), UV and MS were identical between the two compounds. Since the configuration of the compound (1) is *trans*, both the compounds (4a) and (4b) must be *trans*. Consequently, dehydrodiconiferyl alcohol (2), which is the starting material of (4b) must be of *trans* configuration.

### 1.3.2 Configuration of dehydrodi-*p*-coumaryl alcohol

The reduction of the  $\gamma,\gamma'$ -hydroxymethyl groups of dehydrodi-*p*-coumaryl alcohol (3) to methyl groups was tried in the same way. However, the coumaran ring of (3) was sensitive to both the catalytic and hydride reductions, and a ring cleavage compound was easily produced. That is, when the catalytic hydrogenation of (3) was carried out in methanol, the ring cleavage compound (10) was obtained in over 80% yield. It is known that the activity of the catalytic hydrogenation reagent increases more in a polar acidic solvent than in a neutral nonpolar solvent<sup>36</sup>. Therefore, the hydrogenation of (3) was carried out in a mixed solution of methanol/dioxane (1:2) to avoid the ring opening as much as possible and the dihydro compound (11) was obtained quantitatively. These experiments suggested that the  $\alpha$ -position of the coumaran (3) was less stable for nucleophilic attack than that of (2). This is a characteristic property of coumaran (2) in comparison with (3). In contrast to such instability of the coumaran ring  $\gamma$ -sulfonyl group was stable for the hydride attack and the reduction of the  $\gamma$ -sulfonyl group without fission of the coumaran ring was very difficult. Under relatively drastic condition (using about 20 eq. of LAH at room temperature), the ring fission compound (12) was produced as a main product, whereas under the milder condition the starting sulfonate (13) was recovered, and the hydride reduction gave many products containing a trace amount of the desired compound (4c). From these facts, the synthesis of (4c) by one step reduction seemed not to be successful so that the monosulfonate (14) was synthesized and then it was reduced

to the compound (4c) (about 34% yield). Easy opening of the coumaran ring to the compound (13) under such reduction condition suggests that the configuration of the coumaran ring is alterable to the more stable *trans* form by recyclization of the ring fission compound. But, once the ring fission occurs,  $\alpha$ -methine compound must be altered to the  $\alpha$ -methylene one which is no longer capable of cyclization. Therefore, it should be assumed that the compound (4c) obtained without any ring fission through sulfonation and subsequent reduction holds the same configuration with (3).

Table 3. Chemical shifts ( $\delta$ , ppm) and coupling constants (Hz) of protons in 4a, 4b and 4c.

	$\alpha$ -CH-	$\beta$ -CH-	$\gamma$ -CH <sub>3</sub>	$\alpha'$ -CH <sub>2</sub> -	$\beta'$ -CH <sub>2</sub>	$\gamma'$ -CH <sub>3</sub>
4c	5.12, d, J = 9.0	3.20 — 3.60, m	1.34, d, J = 7.0	2.54, t, J = 8.0	1.65, m	0.93, t, J = 7.0
4a, 4b	5.05, d, J = 9.5	3.20 — 3.73, m	1.34, d, J = 7.0	2.51, t, J = 8.0	1.60, m	0.93, t, J = 7.0

d = doublet, t = triplet, m = multiplet

On NMR spectra of both compounds, (4a) and (4c), the chemical shifts and coupling constants of the corresponding protons of side chains were identical with each other. For manifesting the similarity, only signals of the side chains are listed on Table 3. These NMR data suggest the following facts. 1)  $\gamma$ -CH<sub>3</sub> (1.34, J=7.0) of (4a) and (4c) gave the same chemical shifts and coupling constants. If the configuration of (4c) is *cis*, two limited conformations will be conceivable, in which  $\gamma$ -CH<sub>3</sub> group lies on the same plane with A ring (a) or vertical to the A ring (b) as shown in Fig. 15.

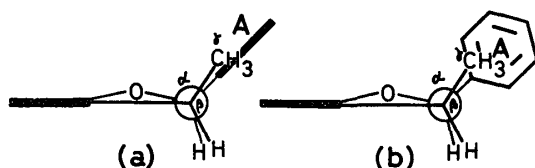


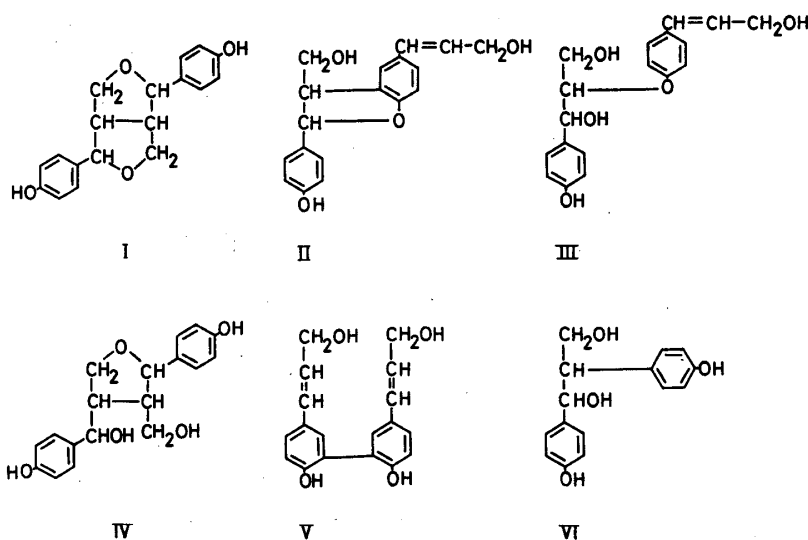
Fig. 15. Two limited conformations of *cis*-coumaran

However, the preferred conformation of both cases seems to be (b), because in the case of (a), a strong steric repulsion exists between  $\gamma$ -CH<sub>3</sub> group and A ring. Consequently, the peak of  $\gamma$ -CH<sub>3</sub> group of *cis* compound would shift to the higher field by the shielding effect of A ring than in the *trans* compound. The signal of  $\gamma$ -CH<sub>3</sub> of (4c) gave almost the same chemical shift and coupling constant as (4a) which has *trans* configuration. Taking into consideration a slight difference in the chemical shifts and coupling constants of the side chain protons by the substituent group on the aromatic ring, the  $\gamma$ -CH<sub>3</sub> of (4c) does not seem to be influenced by such an effect of A ring. On the basis of the above results, it is concluded that dehydrodi-*p*-coumaryl alcohol (3) has the same *trans* configuration with dehydrodiisoeugenol (1). The signals of  $\alpha$ -methine protons of both (2) and (3) at  $\delta$ 5.49 (J=6.0) and  $\delta$ 5.54 (J=5.8)

were shifted to  $\delta 5.05$  ( $J=9.5$ ) and  $\delta 5.12$  ( $J=9.0$ ), respectively, by conversion of the  $\gamma$ -hydroxymethyl groups to methyl groups. This indicates that  $\alpha$ -methine protons are influenced by the deshielding effect of  $\gamma$ -hydroxymethyl groups, especially due to the lone pairs of hydroxyl groups.

#### 1.4 Analysis of dilignols by gas chromatography and NMR spectrometry<sup>37)</sup>

In 1951, Freudenberg *et al.*<sup>14)</sup> reported that *p*-coumaryl alcohol produced a very similar dehydrogenation polymer (DHP) to that of coniferyl alcohol based on the hydrogen uptake by both DHP's and their elementary analysis. Later, Bland *et al.*<sup>15)</sup> reported that artificial lignins prepared from *p*-coumaric acid on potato parenchyma and *Sphagnum* MWL were highly condensed polymers containing double condensations at C-3 and C-5 of the *p*-hydroxyphenyl ring, and suggested the different reactivity between *p*-coumaryl and coniferyl alcohols on dehydrogenation. Recently, Yamasaki *et al.*<sup>16)</sup> reported that no difference of condensation pattern between *p*-coumaryl and coniferyl alcohols was found in their DHP formation from the yield of the condensed and noncondensed type compounds obtained by permanganate and hydrogen peroxide oxidation of the both methylated DHP's.



It seems that this problem is solved more clearly from the yield of the dilignols of the both alcohols. In Section 1-1, the isolation and identification of the four dilignols was described. In this Section, configuration of the dilignol (3) and the yield of these dilignols determined by gas chromatography and NMR spectrometry are described.

##### 1.4.1 Configuration of *p*-hydroxyphenylglycerol- $\beta$ -*p*-coumaryl ether

As described in Section 2-1, guaiacylglycerol- $\beta$ -guaiacyl ether was synthesized in high yield. The ratio (*erythro*/*threo*) of the isomers was about 3:1<sup>38)</sup>. These configurations were determined by comparison with results by Miksche *et al.*<sup>39)</sup> In NMR

spectra of these acetates, the chemical shifts and coupling constants of  $\alpha$ -methine protons were  $\delta 6.12$  (1H, d,  $J=5.0$ , *erythro*) and  $\delta 6.17$  (1H, d,  $J=6.2$ , *threo*) respectively. A doublet peak of  $\alpha$ -CH of *erythro* isomer appeared in higher field and gave a smaller coupling constant than that of *threo* isomer. On the other hand, NMR spectrum of the dihydro acetyl derivative of the dilignol (3) gave two doublet peaks at  $\delta 6.09$  (1H, d,  $J=5.0$ ) and  $\delta 6.13$  (1H, d,  $J=6.2$ ) whose ratio was about 1:5, and this result was also supported by gas chromatography as shown in Fig. 16. The retention times of TMS derivatives of *erythro* and *threo* dihydrodilignols (3) were 47.1 and 49.8 min. Thus, it was concluded that the dilignol (3) was a mixture consisting of *erythro* and *threo* isomers whose ratio was about 1:4.7.

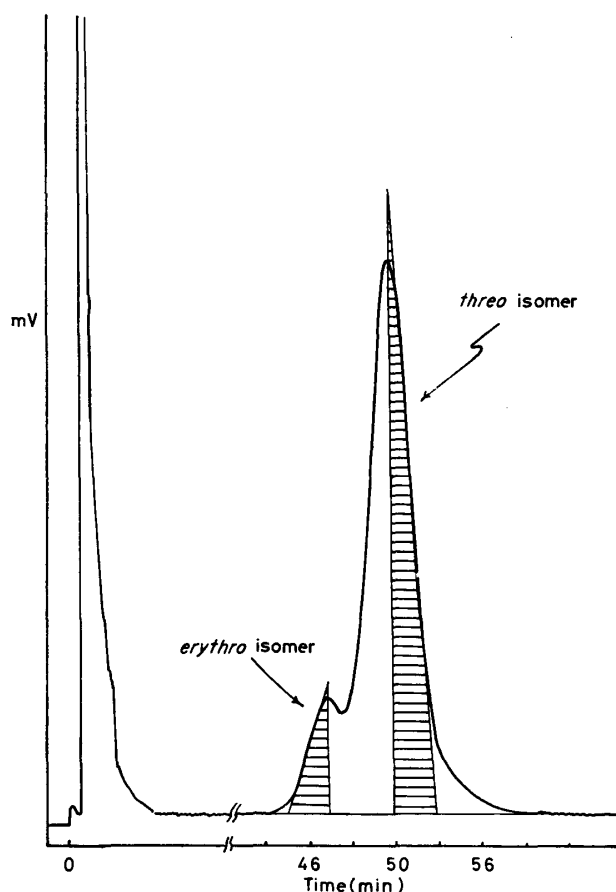


Fig. 16. Gas chromatogram of TMS derivatives of dihydro-dilignol (III).  
Column: 2% OV-17 on Chromororb AW, 2 m-glass column, 200°C.  
Carrier gas: helium. 28 ml/min.

#### 1.4.2 Analysis of dilignols

A dilignol fraction was converted to its hydro-dilignol fraction by catalytic hydrogenation with 5% Pd-carbon and  $H_2$  in dioxane/ethanol (2:1); this catalytic hydrogenation was indispensable from the following two reasons.

First, the peak areas of the propenol dilignols, *e.g.*, dilignol (2) and (3) *etc.*, on the gas chromatogram are not proportional to the amounts of the compounds injected, but only when the propenol side chains are reduced to the propanol side chains, the peak areas of the dilignols are almost proportional to their amounts.

Second, the 5-5'-dilignol (5) seems to be stable when its propenol side chains are converted to the propanol side chains by reductions, as found for the coniferyl 5-5'-dilignol<sup>40)</sup>.

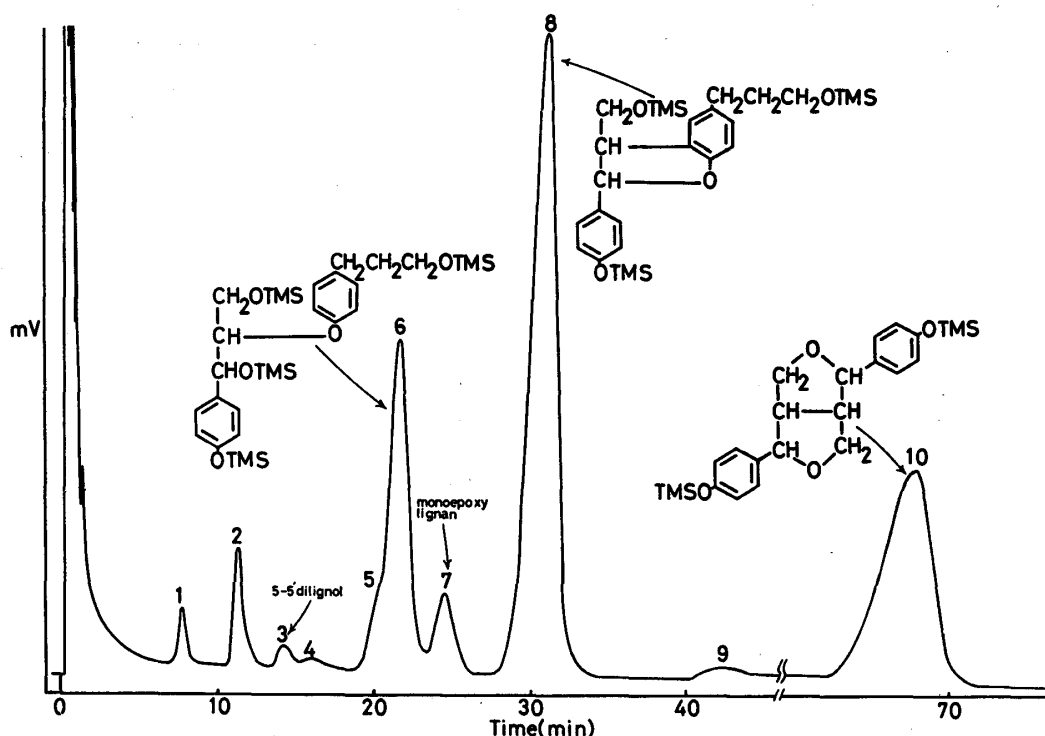


Fig. 17. Gas chromatogram of TMS derivatives of hydro-dilignol fraction obtained by dehydrogenation of *p*-coumaryl alcohol with  $H_2O_2$  and peroxidase system. Column: 2% OV-17 on Chromosorb AW, 2 m, 220°C. Peak 3: tetrahydro dilignol (V), Peak 5: dihydro *erythro* dilignol (III), Peak 6: dihydrop *threo* dilignol (III), Peak 7: monoepoxylignan (IV), Peak 8: dihydro dilignol (II), Peak 10: dilignol (I).

Figure 17 shows the gas chromatogram of TMS derivatives of the hydro-dilignol fraction. Six of ten peaks were identified by comparison with the retention times and mass fragmentation pattern of authentic dilignols. The amounts of the dilignols were calculated from the peak areas, and summarized in Table 4. In Table 4, numbers in column (A) represent the retention times of each peak and those in (B), (C) and (D), peak areas, ratio of the peak areas and product distribution of the three main dilignols, respectively. In the last column (F) is reproduced the product distribution of three main dilignols of coniferyl alcohol which was reported earlier<sup>41)</sup>.

The NMR spectrum of the hydro-dilignol fraction is shown in Fig. 18.  $\alpha$ -Methine

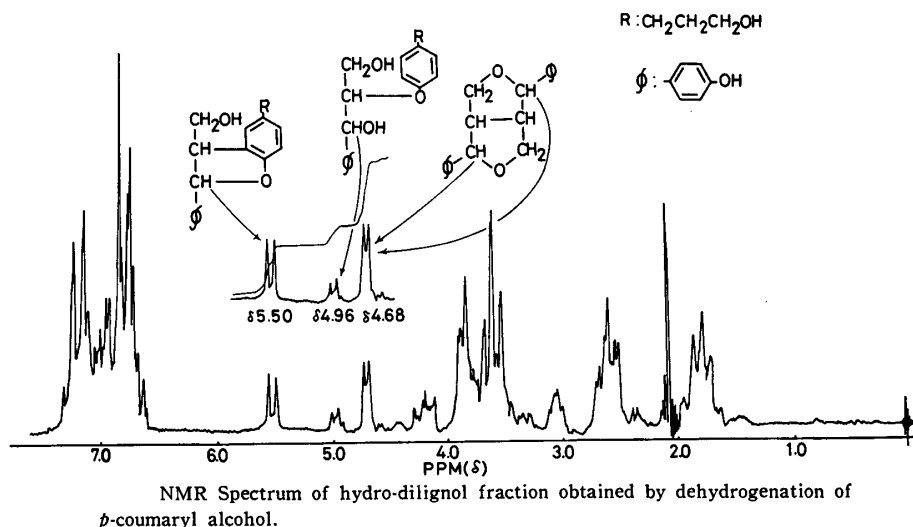


Fig. 18

protons of the three main dilignols (1), (2) and (3) gave the peak at  $\delta 4.68$  (2H, d,  $J=4.0$ ),  $\delta 5.50$  (1H, m) and  $\delta 4.69$  (1H, d,  $J=6.0$ ) respectively, and these peaks were not interfered with other peaks. Therefore, the product distribution of these dilignols may be determined by the integration curve of their  $\alpha$ -methine peaks. The results are given in the column (E) of the Table 4.

Table 4  
Estimation of dilignols by gas chromatography and NMR spectrometry.

Peak number*	A (min.)	B (cm <sup>2</sup> )	C (%)		D (%)	E (%)	F (%)
1	7.7	1.7	1.0				
2	11.2	5.0	3.0				
3	14.2	1.0	0.6				
4	15.8	0.5	0.3				
5	20.0	30.3	18.0		20	20	19
6	21.5						
7	24.4	5.2	3.0	1.0			
8	31.0	76.3	45.0		49	48	54
9	42.0	1.4	0.8				
10	67.5	48.3	28.3	9.4	31	32	27

A: retention time, B: peak area, C: ratio of the peak area, D: ratio of three main dilignols, E: ratio of three main dilignols obtained by NMR analysis, F: ratio of three main dilignols of coniferyl alcohol<sup>9)</sup>.

\* peak number corresponds to those of the compounds in Fig. 17.

These data lead to the following conclusions. TMS derivative of synthetic 1,2-diarylpropane-1,3-diol (6) gives a peak at 5.8 min. on gas chromatogram, but the hydro-dilignol fraction did not give any peak at the same retention time (Fig. 17). Furthermore, *p,p*-dihydroxystilbene which was synthesized from dilignol (6) by alkali degradation could not be found in the alkali degradation products of DHP and dilignol fraction. Therefore the dilignol (6) seems to be formed at a later stage of dehydro-

genation. Only 0.6% of 5-5'-dilignol (5) was detected by gas chromatography, and then the double condensation at C-3 and C-5 reported by Bland *et al.*<sup>15)</sup> may not be possible at this dehydrogenation stage and also at DHP's stage<sup>16)</sup>. The ratio of the *p*-coumarylresinol (1) and monoepoxylignan (4) which were formed by the *racemoid* and *mesoid* couplings at C- $\beta$  and C- $\beta'$  carbons, respectively, was about 9.4:1. Thus, it is expected that coniferyl and sinapyl alcohols give the corresponding monoepoxylignans with the same ratio on dehydrogenation. Investigation on this point, is now in progress. The ratio of the amounts of the three main dilignols (1), (2) and (3) was 31:49:20, respectively by gas chromatography, and the same result was obtained by NMR analysis as shown in column (E) of Table 4. The most reactive radical of the four resonance radicals of both alcohols is the  $\beta$ -radical because the three main dilignols are not formed without participation of  $\beta$ -radical of the side chain. The second reactive one is the radical at 5-position of aromatic ring because the yields of the coumaran type dilignols are larger than that of  $\beta$ -ether type dilignols.

Both *p*-hydroxycinnamyl alcohols, *p*-coumaryl and coniferyl alcohols have a comparable reactivity on enzymic dehydrogenation but a typical difference manifests in the amounts of the coumarans. The percentage of dehydrodiconiferyl alcohol (54%) is larger than that of dehydrodi-*p*-coumaryl alcohol, dilignol (2) (49%), indicating the radical activating effect of the methoxyl group at 3-position of aromatic ring.

### 1.5 Reactivity of quinonemethide<sup>42)</sup>

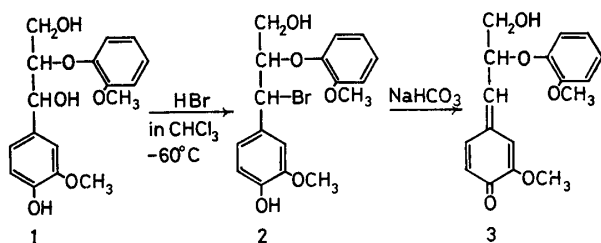
It is well known that quinonemethide intermediates play an important role in the polymerization of lignins. Subsequent to the coupling reactions of mesomeric radicals of *p*-hydroxycinnamyl alcohols, ionic reactions occur between quinonemethides and various nucleophiles. Thus, investigating the reactivity of quinonemethide is indispensable for understanding the mechanism of the polymerization of lignins as has been discussed by Freudenberg *et al.*<sup>13)</sup> and Adler<sup>43)</sup>. Stereochemistry of the products is especially interesting when one chiral center is introduced by the attack of water to quinonemethides as in the formation of  $\beta$ -O-4 dilignols. Sarkanen reported that *threo*  $\beta$ -O-4 dilignol is formed more than *erythro* isomer on the dehydrogenation of isoeugenol<sup>44)</sup>. Our investigations also showed that *threo* isomers are produced more than *erythro* counterparts on dehydrogenation of *p*-coumaryl<sup>37)</sup>, sinapyl and coniferyl alcohols<sup>26)</sup>.

As quinonemethide intermediates are almost a planar molecule, it is considered that water attacks from both sides of the compound with equal probability, giving almost 1.0 in the ratio of *erythro* to *threo* isomers. Sarkanen suggested that the predominant formation of the *threo* isomer is ascribed to steric reasons<sup>44)</sup>. In this Section, based on the reaction of the quinonemethide derived from guaiacylglycerol- $\beta$ -guaiacyl ether with various nucleophiles, factors which affect on the ratio of both isomers are

discussed.

### 1.5.1 Reaction of quinonemethide with various nucleophiles

Quinonemethide (3) was prepared by the method of B. Johansson *et al.*<sup>45)</sup> as shown in Fig. 19. Guaiacylglycerol- $\beta$ -guaiacyl ether (1) synthesized by the method of Nakatsubo *et al.*<sup>38)</sup> was converted to its bromide (2) with hydrogen bromide at  $-60^\circ\text{C}$  in chloroform. The chloroform solution of the bromide (2) was treated with a saturated sodium bicarbonate solution, and a yellow quinonemethide solution which is stable at  $5^\circ\text{C}$  was obtained. A chloroform solution of quinonemethide (Q.M.) was used for the following reactions.



Synthetic route of quinonemethide.

Fig. 19

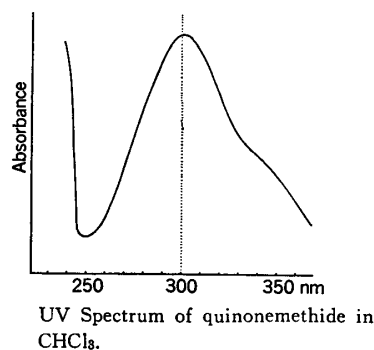


Fig. 20

The UV spectrum of this quinonemethide showed a maximum peak at 301 nm ( $\epsilon=15150$ ) as shown in Fig. 20, and the reaction rate with nucleophiles could be followed by the decreasing rate of absorption at the maximum. The configuration of this reaction products was determined by the analysis of NMR spectra. On the NMR spectrum of triacetyl guaiacylglycerol- $\beta$ -guaiacyl ether (1) the  $\alpha$ -methine doublet peak of the *erythro* isomer appeared at higher field ( $\delta 6.12$ ,  $J=5.0$ ) than that of the *threo* counterpart at  $\delta 6.17$  ( $J=6.2$ ). The  $\alpha$ -methine doublet peak of the *erythro*  $\alpha$ -acetyl derivative of compound (1) which was synthesized by the reaction of Q.M. (3) with acetic acid, appeared at  $\delta 6.02$  ( $J=6.0$ ) and that of the *threo* counterpart at  $\delta 6.11$  ( $J=8.0$ ) as shown in Fig. 21. As  $\beta$ -protons which couple with these  $\alpha$ -protons give peaks in the significantly higher field than  $\alpha$ -methine ones,  $\alpha$ -protons give parallel lines which are of the same height and are not interfered with other peaks. From these considerations, the ratio of *erythro* to *threo* isomers ( $E/T$ ) can be determined by the measurement of the height or integration curve on both side peaks among three peaks. As  $\alpha$ -methine peaks are only important for the determination of the  $E/T$  ratio, the peaks of the products, which were obtained by the reactions between Q.M. (3) and aliphatic carboxylic acids such as formic, propionic, isobutyric and trimethyl acetic acids, are given in Fig. 21. These NMR data indicated that the more bulky nucleophiles give more *erythro* isomers. The relative reaction times and  $E/T$  ratios by various nucleo-



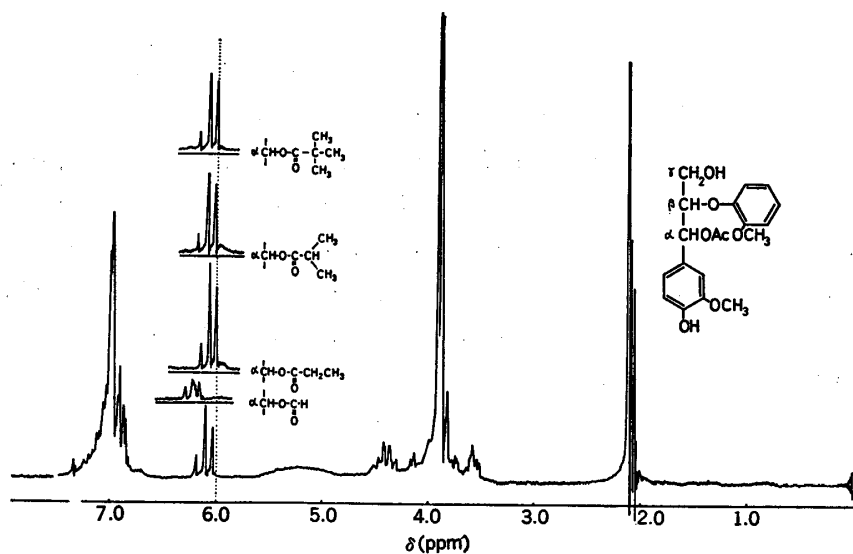
NMR Spectrum of  $\alpha$ -acetyl guaiacylglycerol- $\beta$ -guaiacyl ether.

Fig. 21

Table 5  
Reaction of quinonemethide and  
nucleophiles.

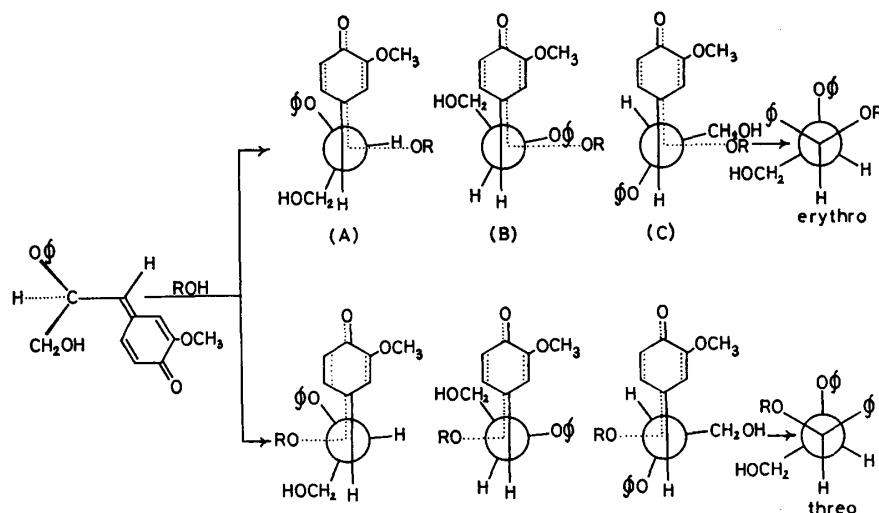
ROH	Relative reaction times	<i>Erythro</i> <i>Threo</i>
HOH		1.1
CH <sub>3</sub> CH <sub>2</sub> OH	$2.1 \times 10^5$	
CH <sub>3</sub> OH	$1.3 \times 10^5$	
(CH <sub>3</sub> ) <sub>3</sub> CCOOH		3.9
(CH <sub>3</sub> ) <sub>2</sub> CHCOOH	$3.2 \times 10^4$	3.8
CH <sub>3</sub> CH <sub>2</sub> COOH	$1.0 \times 10^4$	3.2
CH <sub>3</sub> COOH	$1.8 \times 10^3$	2.6
HCOOH	1	1.6

philes are summarized in Table 5.

These reactions were conducted quantitatively, and all reactions were carried out in chloroform solution of Q.M. (3). The relative reaction times which correspond to the decrease in maximum absorption of Q.M. caused by reaction of the nucleophiles are also listed in Table 5. The stereochemistry of the  $\alpha$ -alkoxy derivatives obtained by reactions of methyl and ethyl alcohols has not been determined. Water reacted with Q.M. in chloroform only in the presence of catalytic amounts of acid (e.g., HCl) because of the two-phase reaction. The reaction with trimethyl acetic acid was very sluggish because of steric hindrance, hence the rates of these two reactions are not listed in Table 5.

The data in Table 5 clearly show that the rate of the reactions is proportional to the acidity of nucleophiles because acids act as substrates for the Q.M. and also as an acid catalyst. On the other hand, the more the steric hindrance of nucleophiles

increases, the more the rate decreases, but the formation of *erythro* isomers increases remarkably. For example, the mixture consisting of *erythro* (80%) and *threo* (20%) isomers was obtained by the reaction of trimethyl acetic acid. Consequently, the  $E/T$  ratio was considerably influenced by the steric hindrance of nucleophiles. This result was also supported by the fact that the reaction with water, which does not give such a steric hindrance, gave a mixture consisting of almost equal amount of the isomers ( $E/T$  ratio was about 1.0).



Possible conformations of quinonemethide in transition state.

Fig. 22

Thus, three limited conformations of the transition state in which the quinonemethide group takes *trans* orientation for each of  $\gamma$ -hydroxymethyl group (A),  $\beta$ -hydrogen (B) and  $\beta$ -phenoxy group (C) respectively, are conceivable as shown in Fig. 22. For each conformation, *erythro* or *threo* isomer is formed by the attack of a nucleophile from the right or left side of the planar quinonemethide group, respectively. In these conformations, (B) may not participate in the reaction because of unstability due to a large steric hindrance existing between Q.M. group and  $\gamma$ -hydroxymethyl or  $\beta$ -phenoxy group. If the reaction proceeds *via* (C)-conformation, *threo* isomer may be preferentially produced, because nucleophiles attack from the same side of  $\beta$ -hydrogen but not from the side of  $\gamma$ -hydroxymethyl group due to the steric hindrance. By a similar steric factor, *erythro* isomer may be formed predominantly *via* (A)-conformation, which favors *erythro* isomers.

However, it has been found that *threo* isomer predominates on enzymic dehydrogenation of *p*-hydroxycinnamyl alcohols<sup>26,37)</sup> and isoeugenol<sup>44)</sup>, and the difference between the reactions should be ascribed to the properties of solvent used. All the reactions described above were carried out in chloroform solution, whereas

enzymic dehydrogenation has been conducted in aqueous solution. Thus, the reaction of Q.M. in aqueous solution was tested. The chloroform solution of Q.M. was evaporated *in vacuo* at 10°C under nitrogen stream, and the residue was dissolved in dioxane. All the reactions discussed below were carried out using dioxane solution of Q.M.

When Q.M. dioxane solution was added dropwise into water, bright yellow color of Q.M. disappeared after 15 min. in dioxane/water (1:9) and 4 hours in dioxane/water (1:1) respectively. Guaiacylglycerol- $\beta$ -guaiacyl ether which was quantitatively obtained, was acetylated with Ac<sub>2</sub>O/pyridine for determination of the configuration by NMR spectrometry. Surprisingly, *E/T* ratio was about 0.5 in dioxane/water (1:9) and 0.4 in dioxane/water (1:1) respectively. These values did not change when phosphate buffer (pH=6.0, 0.05 M) was used instead of water, or when reaction temperature was changed (20°C and 50°C). These results suggest that the *E/T* ratio is determined only by the difference of solvent. As to the reason for variations of *E/T* ratio by the difference of solvent, the following three views might be considered; 1) the difference of the conformation on the transition state in the respective solvents, 2) stability of the products and 3) others, e.g., some hydrogen bonding between Q.M. and nucleophiles.

If the reaction occurs *via* (C)-conformation in water, the more *threo* isomer must be produced by the reaction with acetic acid in water because acetic acid has larger steric hindrance than that of water. Based on this assumption, the reaction was carried out in the equimolar solution of water and acetic acid. Q.M. (0.16 mM) dissolved in dioxane (1 ml) was added dropwise at 20°C into a mixture of water (1.98 g, 0.11 M) and acetic acid (6.6 g, 0.11 M) with stirring. Almost equimolar mixture of  $\alpha$ -hydroxy and  $\alpha$ -acetyl derivatives which were formed by the attack of water and acetic acid to the Q.M., respectively, was obtained. Unexpectedly, the *E/T* ratios of  $\alpha$ -hydroxy and  $\alpha$ -acetyl derivatives were about 0.66 and 1.0 respectively. Therefore, the Q.M. reaction in water does not proceed *via* (C)-conformation, and the first view is ruled out. However, it is noteworthy that the formation of *threo* isomer increases by the exchange of chloroform for water in both reactions of water and acetic acid.

The next step, the isomerization reaction of a crystalline *erythro* isomer of guaiacylglycerol- $\beta$ -guaiacyl ether (1) was carried out in order to determine the thermodynamic stability of *threo* and *erythro* isomers. *Erythro* guaiacylglycerol- $\beta$ -guaiacyl ether (1) was dissolved in dioxane/water (9:1) containing 0.2 N HCl and heated at 50°C for 1, 12 and 24 hours (condition of mild acidolysis<sup>46</sup>). The reaction product in each case gave one spot, with the same *R<sub>f</sub>* value as starting compound. on silica gel tlc plate developed with 5% methanol/chloroform. After acetylation, the *E/T* ratio in respective reactions were determined to be about 9.0, 1.0 and 1.0, showing

that the isomerization was completed in 12 hours. These results indicate that thermodynamic stabilities are not different between *erythro* and *threo* isomers. Thus, the  $E/T$  ratio on the reaction of Q.M. in water is not determined by the product development control<sup>47)</sup>, and the second view must be ruled out.

Finally, it was proved from the results described above that the attack of water in aqueous solution is not controlled by a steric factor, thermodynamic stability of the products or salt effect of buffer. However, water actually approaches preferentially to the almost planar Q.M. molecule from the favorable side for the formation of *threo* isomer. This suggests the formation of some attracting force, such as a hydrogen bonding between two molecules on the transition state of the reaction. Among five oxygens in the Q.M. molecule, ketonic, methoxyl and  $\gamma$ -CH<sub>2</sub>OH groups may be ruled out because the *threo* isomer predominates on dehydrogenation of isoeugenol which has  $\gamma$ -CH<sub>3</sub> group, instead of  $\gamma$ -CH<sub>2</sub>OH. Therefore, a hydrogen bonding formed with oxygen of  $\beta$ -phenoxy group might be important for the control of the  $E/T$  ratio.

It is concluded that water attacks preferentially from the same left side with  $\beta$ -phenoxy or  $\beta$ -hydroxyl (in the case of the formation of arylglycerols) group of quinonemethide *via* (A)-conformation by forming a hydrogen bonding between a hydrogen of water and oxygen of  $\beta$ -phenoxy or  $\beta$ -hydroxy group, resulting in predominant *threo* isomer on enzymic dehydrogenation. The results also suggest that such a hydrogen bonding factor participates in the polymerization of lignins.

## 2. Syntheses of a lignin model compound and oligolignols

### 2.1 Synthesis of guaiacylglycerol- $\beta$ -guaiacyl ether<sup>38)</sup>

Arylglycerol- $\beta$ -aryl ether substructure is one of the most important interphenylpropane linkage in lignins and it has been reported that the structure comprises about 30 to 50% of the phenylpropane units<sup>33,48)</sup>. Therefore, guaiacylglycerol- $\beta$ -guaiacyl ether (1) has been used as an important model compound for various reactions of lignin such as pulping processes.

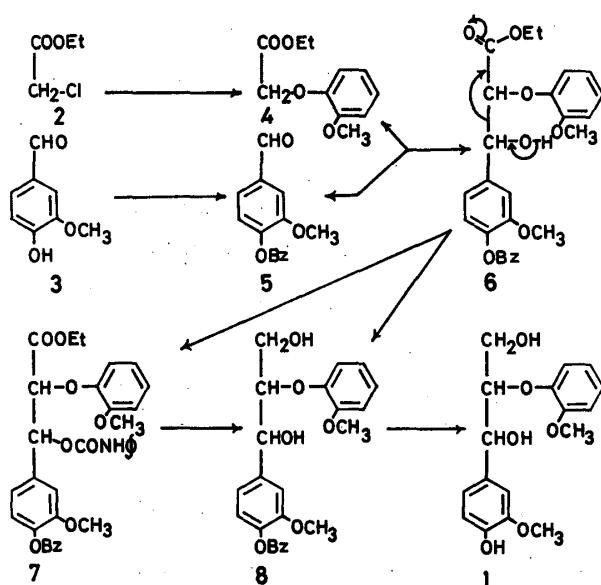
This compound (1) has been synthesized by Adler *et al.*<sup>49)</sup>, Kratzl *et al.*<sup>50)</sup> and Miksche *et al.*<sup>39)</sup> *etc.* However, the synthetic method by these investigators required many reaction steps in a linear synthesis and the overall yield of the product was low. The method proposed by Miksche *et al.*<sup>39)</sup> requires the most steps although both the *erythro* (75%) and *threo* (10%) isomers of the  $\beta$ -hydroxy ester were obtained as crystals by the reduction of  $\beta$ -keto ester, and then the final compound (1) was also obtained as crystals by this method.

Since the compound (1) has been of increasing use for the reaction and chemical elucidation of lignin, a synthetic method by which the compound (1) is obtained in high yield and by shorter reaction steps is necessary.

A new convergent synthesis of the  $\beta$ -hydroxy ester (6), one of the intermediate in the method by Miksche *et al.*<sup>39)</sup> is described in this Section.

### 2.1.1 A new convergent synthesis of the compound

The compound (6) which is a  $\beta$ -hydroxy ester is expected to be cleaved to the compounds (4) and (5) by a retro aldol condensation type reaction as shown in Fig. 23. Thus, it is assumed that the compound (6) can be synthesized through the reverse reaction from the compound (4) which is obtained from commercially available ethyl chloroacetate (2) and benzyl vanillin (5). Along the above described synthetic route, the following experiments were carried out.



Synthetic Route of Guaiacylglycerol- $\beta$ -guaiacyl Ether

Fig. 23

The compound (4) was synthesized in quantitative yield by stirring ethyl chloroacetate (2) and guaiacol in acetone at room temperature in the presence of potassium iodide and potassium carbonate. In this case, the absence of potassium iodide decreased the reaction rate. The compound (4) which was determined by NMR and IR spectra was obtained as a pure oil by distillation under reduced pressure in ca. 70% yield. A singlet peak appeared at  $\delta$ 4.66 in NMR, and the IR spectrum showed the presence of the carbonyl band at  $1780\text{ cm}^{-1}$ .

It is assumed that even if the compound (6) could be synthesized by the condensation of (4) and (5) under drastic conditions, the compound would be converted immediately to an  $\alpha,\beta$ -unsaturated ester. On the other hand, under mild conditions using the same base, the condensation does not proceed. In fact, this was reported earlier by Freudenberg *et al.*<sup>51)</sup> in a convergent synthesis of the  $\beta$ -hydroxy ester. That is, when the condensation was carried out at the reflux temperature of ether using

sodium as the base, the  $\alpha,\beta$ -unsaturated ester was obtained in high yield, while the  $\beta$ -hydroxy ester obtained in low yield at a low temperature ( $0^\circ\text{C}$ ). The low yield of the  $\beta$ -hydroxy ester suggests that the self-condensation of the  $\alpha$ -phenoxy acetate proceeded under their reaction condition in addition to the conversion of the  $\beta$ -hydroxy ester to the  $\alpha,\beta$ -unsaturated ester, although the reason for this low yield was not described in their paper. The present investigation indicated that the enolate anion of the compound (4) was liable to self-condensation. Therefore, this reaction step should be carried out at low temperature. Furthermore, as the  $\alpha$ -hydrogens of the ester are less acidic than those of aldehyde and ketone groups, the stronger bases should be used for synthesis of  $\alpha$ -carbanion of ester.

Considering these facts, the condensation reaction which is the key step in this synthetic route must be carried out under mild conditions at low temperature, and under such conditions the carbanion of the compound (4) must be synthesized in high yield. Thus, it is assumed that lithium diisopropyl amide satisfies such conditions. Actually, Cregge *et al.*<sup>52)</sup> reported the alkylation of  $\alpha$ -position of the ester in high yield using this reagent. But an example such as the condensation reaction between  $\alpha$ -phenoxy ester and aldehyde has not so far been reported.

Table 6. Effect of reaction conditions on the yield of *erythro* and *threo* isomers.

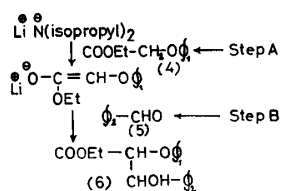
Condition	Solvent	Temp. ( $^\circ\text{C}$ )		Yield %	<i>erythro</i> / <i>threo</i>
		Step A	Step B		
I	$\text{Et}_2\text{O}$	$-30$	$-70$	30	0.8
II	$\text{Et}_2\text{O}$	$-70$	$-70$	70	0.8
III	THF	$-70$	$-70$	85	3.5
IV	THF	$-70$	$-70$	77	3.0
V	THF	$-70$	$-70$	90	3.5
VI	THF	$-74$	$-74$	95	3.5

Condition I—V: methyl lithium/ether solution was used as the base

Condition VI: *n*-butyl lithium/*n*-hexane solution was used as the base

Condition IV: 1.0 eq. of hexametapol was added

Condition V: 1.2 eq. of the compound (4) was added



In the present investigation, the reaction sequence was considered to be divided into two steps, synthesis of carbanion (Step A) and condensation between the carbanion and the aldehyde (Step B) as shown in Table 6. The ratio of geometrical isomers in the reaction mixture and the yield of the  $\beta$ -hydroxy ester (6) from the aldehyde

were determined by the NMR spectra. The  $\alpha$ -protons of the  $\beta$ -hydroxy ester (6) and aldehydic proton of benzyl vanillin gave doublets at  $\delta$ 4.48 (*threo*) and  $\delta$ 4.71 (*erythro*) and a singlet at  $\delta$ 9.98, respectively. These peaks were not interfered with the other peaks. The results are summarized in Table 6. Under condition I-V, ether solution of methyl lithium was used, and *n*-hexane solution of *n*-butyl lithium was used under the condition VI. From these results, the following points are indicated.

First, when step A was carried out at  $-30^{\circ}\text{C}$ , the yield of the compound (6) was only 30% and the self-condensation product of the compound (4) was found. The results indicated that the self-condensation of the compound (4) proceeded at such a temperature. In fact, it has been reported that by Cregge *et al.*<sup>54)</sup> that the self-condensation of methyl acetate was found even under  $-78^{\circ}\text{C}$ , which was avoided by using *t*-butyl ester. Thus, self-condensation is supposed to be avoided by using the ester with a large steric hindrance. However, this was not available for the present investigation, and then the reaction had to be carried out under the temperature as low as possible. Thus, the temperature was kept below  $-70^{\circ}\text{C}$ , and self-condensation was avoided.

Second, the ratio of *threo* and *erythro* isomers depended on the solvent used. The ratio (*erythro*/*threo*) was about 0.8 and 3.0 in ether and tetrahydrofuran, respectively. These values varied somewhat with changes in experimental condition. It seemed that the ratio was proportional to the yield of the  $\beta$ -hydroxy ester (6), and in tetrahydrofuran the increase in the yield of compound (6) paralleled that of the *erythro* isomer. There is no definite explanation for this result at present. However, it seems that the results are due to differences of the transition state of the condensation reaction in both solvents. Considering the experimental conditions described above, the reaction was carried out under optimum condition, that is, *n*-butyl lithium in hexane solution was used as base in tetrahydrofuran at  $-74^{\circ}\text{C}$ . Under this condition, the mixture of *erythro* (75%) and *threo* (25%) isomers in 95% yield could be obtained in which only *erythro* isomer was crystallized in 51% yield. Since the mother liquor, consisting of the mixture of isomers, did not crystallize, the compound was converted to its carbamate (7) which easily crystallized from ether in 70% yield. Although the acetate and carboethoxy derivatives of the compound (6) were also prepared, these derivatives did not crystallize. At this step, about forty five grams of the  $\beta$ -hydroxy ester (6) was easily obtained by one reaction. The  $\beta$ -hydroxy ester (6) was reduced with lithium aluminum hydride to the compound (8) which was converted in almost quantitative yield to the final compound (1) by catalytic hydrogenation. The *erythro* isomer of the compound (1) was crystallized from ethyl acetate. Melting points of the compound (1) and its triacetate were  $94-95^{\circ}\text{C}$  and  $107^{\circ}\text{C}$ , respectively, which were identical with those obtained by Miksche *et al.*<sup>39)</sup> The carbamate (7) was also

treated as described above and the mixture of stereoisomers of the compound (1) was obtained in almost quantitative yield as a colorless foaming substance which gave one spot on tlc developed with 5%-methanol/chloroform. The overall yield of the final compound (1) from benzyl vanillin was about 72%.

## 2.2 Syntheses of guaiacylglycerol- $\beta$ -coniferyl and $\beta$ -coniferyl aldehyde ethers<sup>53)</sup>

Arylglycerol- $\beta$ -aryl ether substructure is the most important structure in lignins as described in Section 2-1. Guaiacylglycerol- $\beta$ -guaiacyl ether has been used as a lignin model compound for studying various lignin reactions. However, this compound is not truly representative of the lignin structure, because the  $\beta$ -aryl ether residue in lignins contain C<sub>3</sub>-side chains. To study the effect of chemical changes on functional groups in the side chains of  $\beta$ -aryl ether substructure, it is desirable to use structural models containing allyl alcoholic or allyl aldehyde type side chains, which do occur in lignins. Guaiacylglycerol- $\beta$ -coniferyl (5) and  $\beta$ -coniferyl aldehyde (4) ethers, therefore, are suitable model compounds. These compounds (4) and (5) have been isolated in low yield as lignin hydrolysis products<sup>54,55)</sup>, and as products formed by the oxidative coupling of coniferyl alcohol<sup>19,56)</sup>. However, the separation and purification of the two ethers are difficult because many other products are formed in both hydrolysis and dehydrogenation, and compounds are obtained as a mixture of *erythro* and *threo* isomers which cannot be purified by crystallization. The synthesis of guaiacylglycerol- $\beta$ -coniferyl ether in low yield has been reported by Freudenberg *et al.*<sup>57)</sup>.

In this Section, the novel synthetic method for preparing guaiacylglycerol- $\beta$ -coniferyl and  $\beta$ -coniferyl aldehyde ethers with high yield is described.

### 2.2.1 A new high yield syntheses of the compounds (4) and (5)

The synthetic method for the target ethers is analogous to that used to prepare guaiacylglycerol- $\beta$ -guaiacyl ether described in Section 2-1. For the present syntheses (Fig. 24), coniferyl aldehyde is used as the starting materials instead of guaiacol.

The condensation of compound (1) with (2) by use of lithium diisopropyl amide (LDA) gave the expected compound (3), with small amounts of the starting materials and polar impurities. Purification by silica gel tlc (PF-254 Merck), developed with ethyl acetate/*n*-hexane (1:1), gave the pure compound (3). The use of silica gel chromatography (Wako gel C-100) for large-scale preparation, resulted in a partial deacetalization. Thus, the purification was carried out after the subsequent LAH reduction or at the stage of compound (4). The structure of compound (3) was substantiated by IR, which shows the absorption of the ester group at 1760 cm<sup>-1</sup>, and by NMR spectra. The compound (3) is a mixture consisting of the *erythro* and *threo* isomers; the ratio was found to be about 3.5:1.0 by the NMR spectrum, which showed



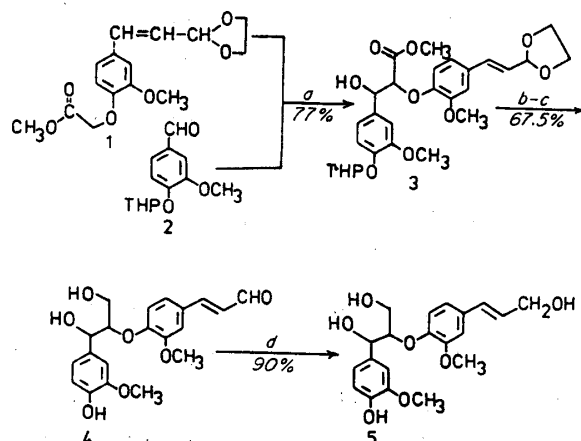
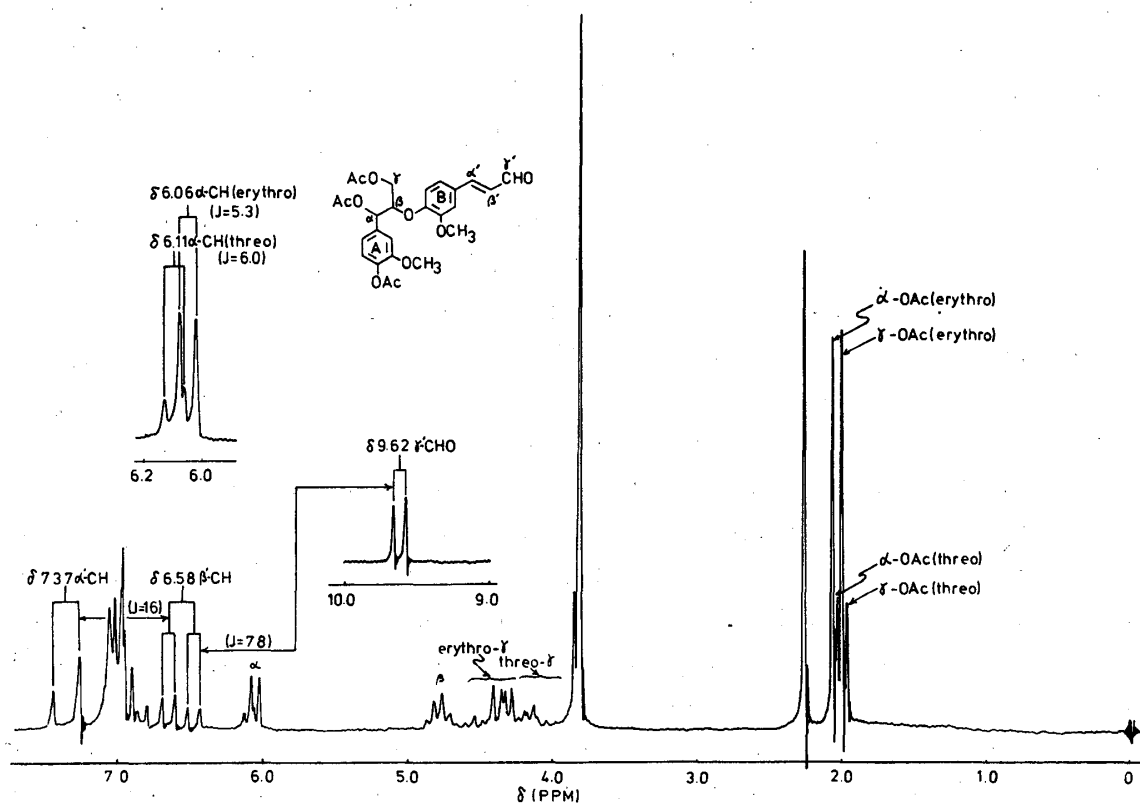


Fig. 24. Synthetic route for guaiacylglycerol- $\beta$ -coniferyl (5) and  $\beta$ -coniferyl aldehyde (4) ethers. <sup>a</sup>Lithium diisopropyl amide/THF/ $-78^{\circ}\text{C}$ . <sup>b</sup> $\text{LiAlH}_4$ /THF/ $50^{\circ}\text{C}$ . <sup>c</sup>1 N-HCl/THF/ $0^{\circ}\text{C}$ . <sup>d</sup> $\text{NaBH}_4$ /MeOH/ $0^{\circ}\text{C}$ .

clearly distinguishable peaks of the ester protons at  $\delta 3.55$  (s, *threo*) and  $\delta 3.68$  (s, *erythro*) and of the  $\alpha$ -methine protons at  $\delta 4.48$  (d,  $J=6.0$ , *threo*) and  $\delta 4.66$  (d,  $J=5.3$ , *erythro*). The *erythro* isomer might be expected to predominate from the reaction mechanism involving a six-membered transition state intermediate.



NMR spectrum of acetylated guaiacylglycerol- $\beta$ -coniferyl aldehyde ether (4)

Fig. 25

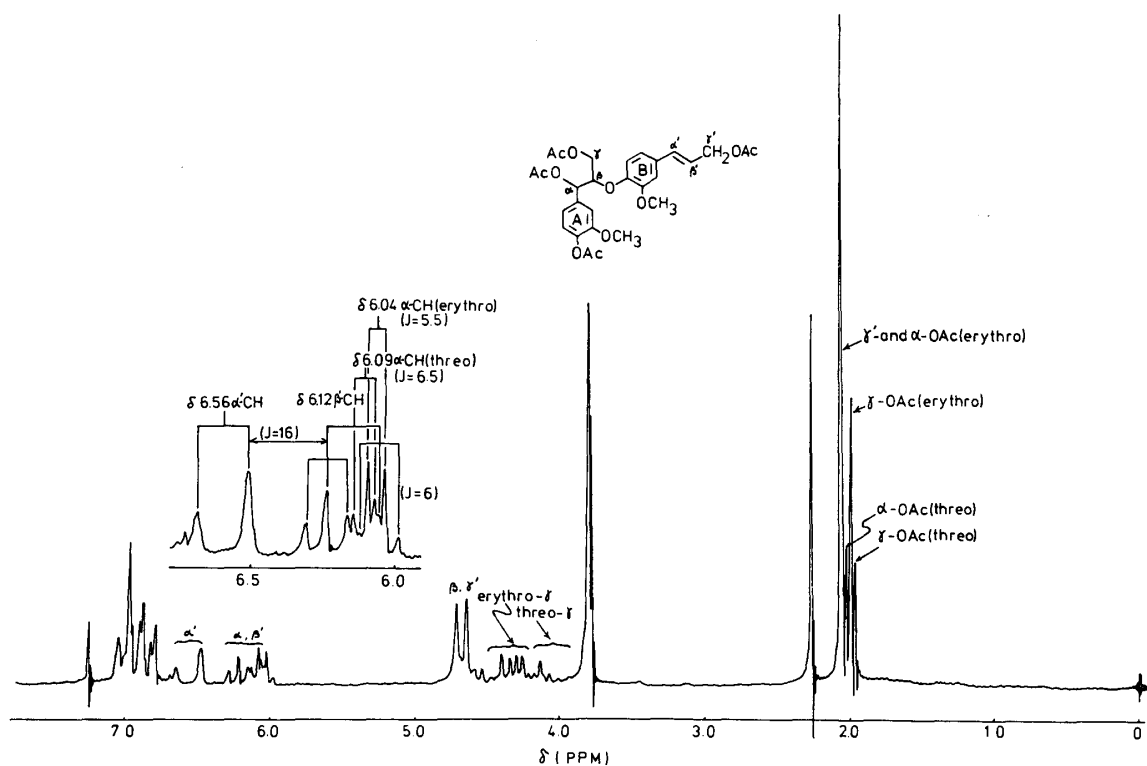
NMR spectrum of acetylated guaiacylglycerol- $\beta$ -coniferyl ether (5)

Fig. 26

Compound (3) was subjected sequentially to lithium aluminum hydride reduction in THF at 50°C (75%), and to hydrolysis with 1N-HCl/THF (1:2) at 0°C (90%) to afford the expected compound (4). The yield of compound (4) from the starting material (1) was about 52%. Compound (4) and (5) were supported by UV, IR, MS and NMR spectra. The NMR spectra of the acetyl derivatives are shown in Figs. 25 and 26. It is noteworthy that the peaks of the  $\alpha$ -methine,  $\gamma$ -methylene and  $\alpha,\gamma$ -alcoholic acetyl are clearly distinguishable between the *erythro* and *threo* isomers in the NMR spectra. The assignment of these protons is based on the presumed reaction mechanism, which gives predominantly the *erythro* isomer, and also by comparison with the NMR spectra of compound consisting of *erythro*/*threo* (about 1.0:1.1) obtained by the oxidative coupling of coniferyl alcohol.  $\alpha$ -Methine and also  $\gamma$ -alcoholic acetyl protons of *erythro* isomers appear at lower magnetic fields than these in the *threo* isomers.

### 2.3 Syntheses of 1,2-diarylpropane-1,3-diols and determination of their configurations<sup>58)</sup>

1,2-Bis-(4-hydroxy-3-methoxyphenyl)-propane-1,3-diol which is one of the typical structural mode in lignin was synthesized by Lundquist *et al.*<sup>59)</sup> The key step of their synthetic method is benzoin condensation of benzyl vanillins,  $\gamma$ -hydroxymethyl group is derived by aldol condensation with formaldehyde, and the 1,3-diol compound

was obtained as a colorless foaming substance consisting of *threo* and *erythro* isomers. However, it is difficult to synthesize the 1,3-diol compounds containing different aryl groups by this method. Although the syntheses of many asymmetric benzoin were reported<sup>60)</sup>, it has not been known whether the condensation reaction between each of vanillin, syringaldehyde and *p*-hydroxybenzaldehyde occurs or not. If this reaction would occur, it is still unknown whether only the desired asymmetric benzoin of the possible benzoin is synthesized and can be isolated. Therefore, their synthetic method does not seem a general one for the syntheses of 1,2-diarylpropane-1,3-diols. Since some 1,2-diarylpropane-1,3-diol compounds containing different aryl groups have been isolated<sup>61)</sup>, a new synthetic method which is applied to any combination between different aryl groups is required for identifications and studies of their chemical properties.

In this Section, the synthesis of 1-(4-hydroxy-3,5-dimethoxyphenyl)-2-(4-hydroxy-3-methoxyphenyl)-propane-1,3-diol (1) by the general synthetic method of 1,2-diarylpropane-1,3-diol is described.

### 2.3.1 A new general synthetic method of the compound

The key step of this synthetic method is the formation of  $\alpha,\beta$ -carbon-carbon bond by condensation of methyl benzylhomovanillate (3) with benzyl syringaldehyde (4). Methyl benzylhomovanillate (3) was synthesized in over 80% yield by oxidative rearrangement, treating benzyl vanilloylmethylketone (2) with thallium (III) nitrate and 70% perchloric acid in methanol at room temperature. This synthetic method reported by Mckillop *et al.*<sup>62)</sup>, is superior to the method reported earlier<sup>63)</sup>. The *p*-hydroxyphenyl analogue was also synthesized by this method.  $\beta$ -Hydroxy ester (5) was synthesized from the homo acid ester (3) in about 70% yield using lithium diisopropyl amide as base. The reaction was carried out in anhydrous THF below  $-70^{\circ}\text{C}$  and unreacted starting compounds were removed by silica gel column chromatography with chloroform as eluent. The eluate gave colorless needles in about 18% yield (5a, *erythro* isomer,  $R_f=0.18$ , developed with ether/*n*-hexane=1:1 on silica gel plate) and colorless prisms from the mother liquor in about 54% yield (5b, *threo* isomer,  $R_f=0.09$ , developed with the same solvent and plate). The ratio of the

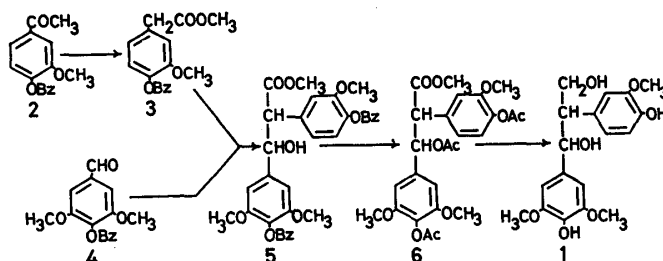


Fig. 27. Synthetic route for 1,2-diarylpropane-1,3-diol.

amounts of (5a) and (5b) is about 1:3. The  $\beta$ -hydroxy esters (5a) and (5b) were converted to the final compounds (1a) and (1b) by subsequent experiments described below. Preliminarily, the compound (5a) was reduced with lithium aluminum hydride and hydrogenated with 5% Pd-carbon and hydrogen, but the desired end product (1a) could not be obtained because of the formation of by-products on the hydride and catalytic reductions. Therefore, the synthesis of the diol (1) was carried out along the route shown in Fig. 27. The compounds (5a) and (5b) were hydrogenated with 5% Pd-carbon and hydrogen in dioxane/ethanol (1:1) and acetylated subsequently with acetic anhydride and pyridine, and triacetyl esters (6a) and (6b)

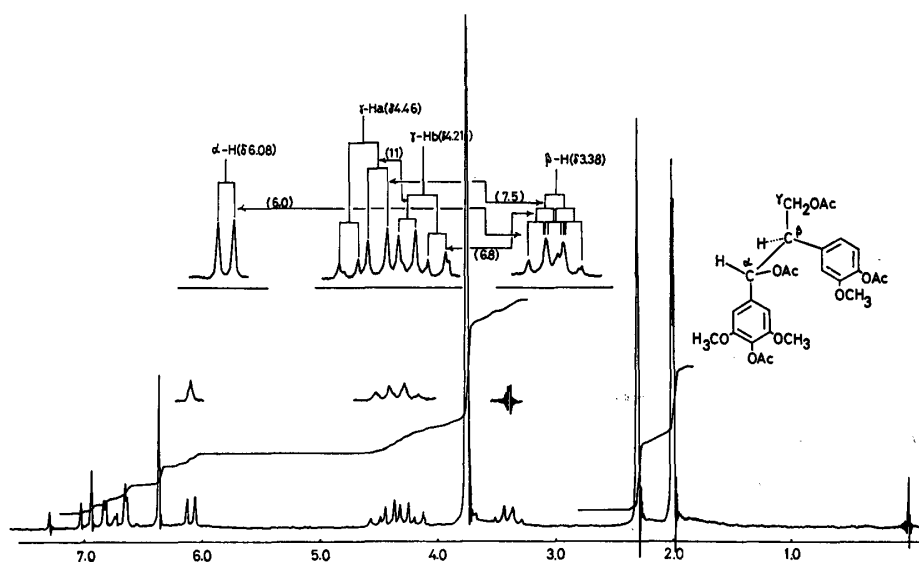


Fig. 28. NMR spectrum of tetraacetate of *erythro*-1,2-diarylpropane-1,3-diol (1a).

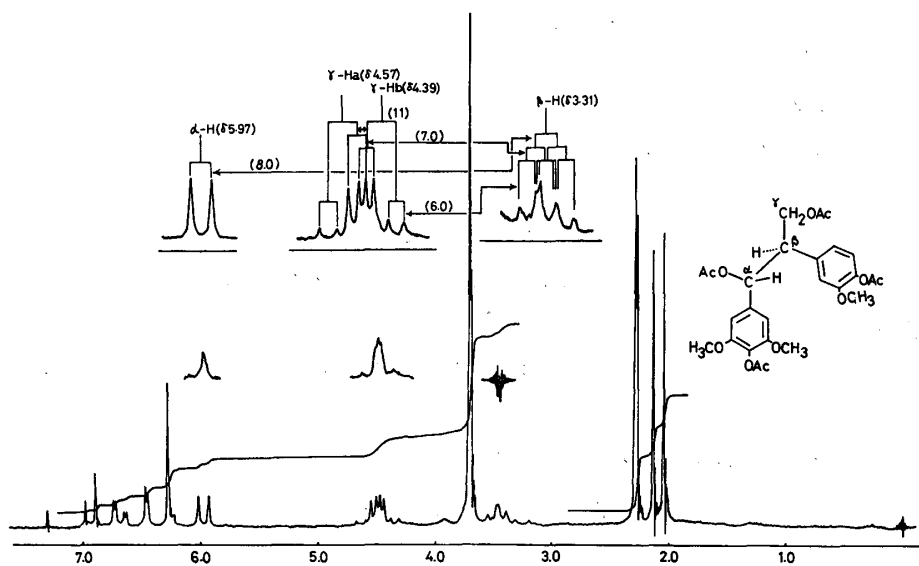


Fig. 29. NMR spectrum of tetraacetate of *threo*-1,2-diarylpropane-1,3-diol (1b).

were obtained in over 95% yield, respectively. The triacetyl esters were then converted to the 1,2-diarylpropane-1,3-diols, (1a, *erythro* isomer and 1b, *threo* isomer) in about 80% yield, by reduction with LAH in THF at 50°C. The structures of these compounds were determined by NMR, MS, IR, UV spectra and elementary analysis.

The NMR spectra of the tetraacetates of these *erythro* (1a) and *threo* (1b) compounds are shown in Fig. 28 and 29, respectively. Each peak was determined by the decoupling method, and the results are visualized in the same Figs. The aromatic protons of the both compounds gave sufficiently separated peaks, and these spectra showed the same pattern except for the difference of the acetyl proton region (at  $\delta$ 1.90 to  $\delta$ 2.30). That is, the peak of  $\alpha$ -acetoxy group of the acetyl compound of (1a) gives almost the same chemical shift as that of  $\gamma$ -acetoxy group, and therefore, the acetoxy protons of the *erythro* isomer (Fig. 28) gives almost two peaks, while the *threo* isomer (Fig. 29) gives three peaks. From these characteristics, the three 1,2-diarylpropane-1,3-diols reported by Nimz<sup>61)</sup> were all determined to be *erythro* isomers.

### 2.3.2 Determination of the configuration by NMR spectrometry

Since guaiacylglycerol- $\beta$ -guaiacyl ether (7) and 1,3-propanediol (1) have the same 1,3-dihydroxypropane structure, the reagent which reacts with the 1,3-dihydroxyl groups of the  $\beta$ -aryl ether (7) is supposed to react with those of the compound (1). Thus, the configurations of these derivatives might be determined by NMR spectrometry. The configuration of the compound (7) has been determined by Gierer *et al.*<sup>64)</sup> based on the fact that the borate complex of the *threo* isomer moved faster than that of the *erythro* isomer in paper electrophoresis.

It seems that if conformation of the compound (7) is fixed through the six-membered ring structure by cyclic ester formation between the 1,3-dihydroxyl groups of the compound (7) and phenyl boronic acid, its configuration and also conformation will be determined by NMR spectrometry. The phenylboronate (8) could be synthesized in quantitative yield by refluxing equimolar amounts of the compound (7) and phenylboronic acid in benzene for 4 hours without any acidic catalyst. The phenylboronate (8) thus obtained was stable and purified by preparative tlc. The phenylboronate group could be removed easily by treating the ester with 1,3-propanediol in a suitable solvent at room temperature<sup>65)</sup>. Moreover, the phenylboronates obtained from a mixture of *erythro* (7a) and *threo* (7b) isomers which could not be separated on the silica gel tlc plate developed with various solvent systems, gave separable spots on the silica gel plate developed with 1.5% methanol/chloroform, and each isomer could be obtained as a pure substance, respectively.

NMR spectra of these phenylboronates (8a) and (8b) are shown in Figs. 30 and 31. On NMR analysis, the following two points have to be noted. These six-membered ring compounds may prefer the stable chair forms, and furthermore the

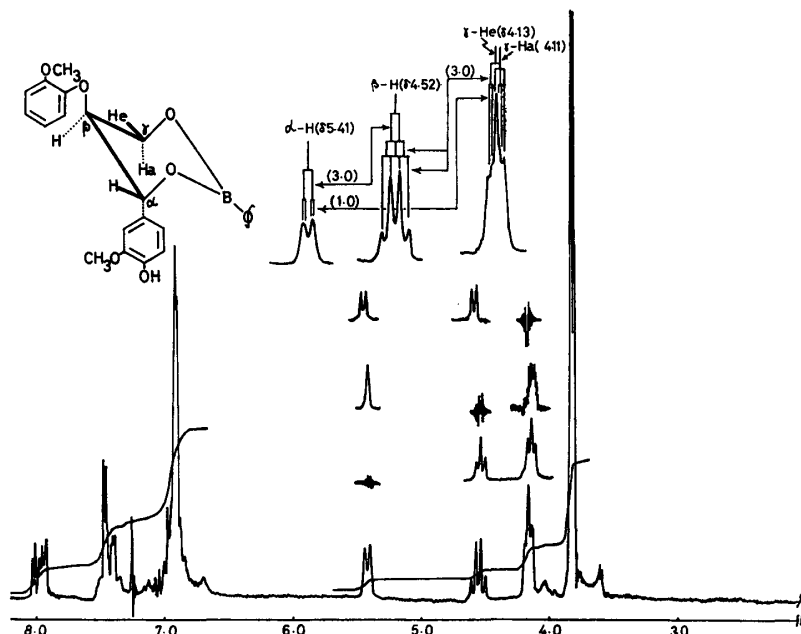


Fig. 30. NMR spectrum of phenylboronate of *erythro*-guaiacylglycerol- $\beta$ -guaiacyl ether (8a).

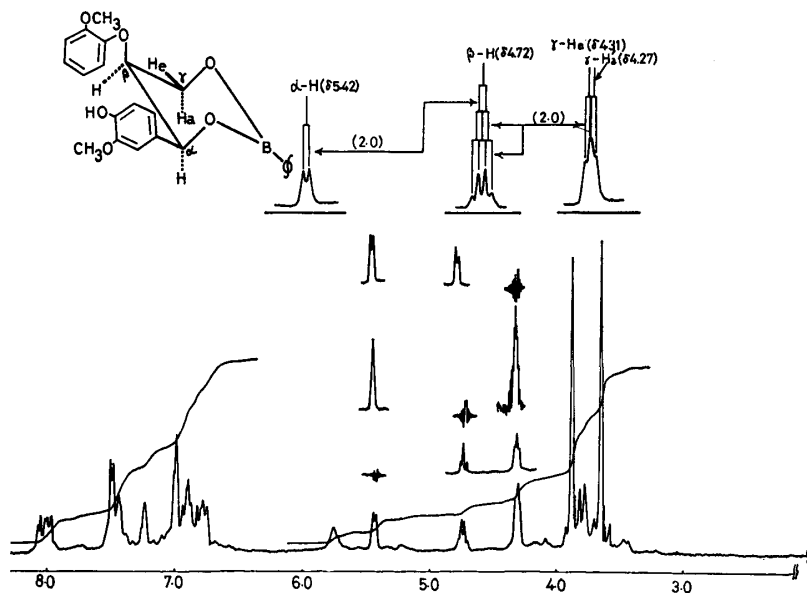


Fig. 31. NMR spectrum of phenylboronate of *threo*-guaiacylglycerol- $\beta$ -guaiacyl ether (8b).

coupling constant ( $J$ ) between  $\beta$ - and  $\gamma$ -axial protons may be almost 10 cps ( $\nu\beta\text{H}$ ,  $\gamma\text{-Ha}=180^\circ$ ) when the  $\beta$ -proton takes axial orientation. Respective peaks of the phenylboronate (8a) were assigned by the decoupling method as shown in Figs.

The  $\beta$ -proton gave a quartet at  $\delta 4.52$  whose coupling constants were  $J\beta\text{H}$ ,  $\alpha\text{H}=J\beta\text{H}$ ,  $\gamma\text{He}=J\beta\text{H}$ ,  $\gamma\text{Ha}=3.0$  cps, indicating equatorial orientation. The quartet peak of the  $\beta$ -proton changed to a triplet, and in addition, the  $\gamma$ -proton peak gave surprisingly

a triplet when a doublet peak of  $\alpha$ -proton, at  $\delta 5.41$ , was irradiated. Such results indicated the occurrence of a long range coupling between  $\alpha$ - and  $\gamma$ -equatorial protons. Thus, the equatorial orientation of  $\alpha$ -proton was determined, and the *erythro* configuration and the conformation of the compound (8a) were determined as shown in Fig. 30. NMR spectrum of the compound (8b) gave the same pattern as that of the compound (8a). But a long range coupling between  $\alpha$ - and  $\gamma$ -He protons was not found in this case suggesting the axial orientation of  $\alpha$ -proton. The small coupling constants,  $J\beta H, \alpha H = J\beta H, \gamma Ha = J\beta H, \gamma He = 2.0$  suggest equatorial orientation of the  $\beta$ -proton. Such configuration was also supported by the high-field shift of one of the methoxyl groups, which is attributable to the  $\beta$ -orientations of both  $\alpha$ -phenyl and  $\beta$ -phenoxy groups. Therefore, the compound (8b) is unequivocally *threo* isomer and takes the conformation shown in Fig. 31. Thus, the configuration of guaiacylglycerol- $\beta$ -guaiacyl ether (7) was determined by NMR spectrometry of only one phenylboronate isomer.

Similarly, the stereochemistry of the 1,2-diarylpropane-1,3-diol (1) is discussed. The phenylboronates of the compound (1a) and (1b) were synthesized by the same method, and these NMR spectra are shown in Figs. 32 and 33, respectively. Neither NMR spectra showed any long range coupling between  $\alpha$ - and  $\gamma$ -He protons reflecting the axially oriented  $\alpha$ -protons. Large coupling constants,  $J\beta H, \alpha H = J\beta H, \gamma Ha = 10$  cps on the NMR spectrum of the compound (9b) shown in Fig. 33, suggests that the dihedral angles between these protons are  $180^\circ$ , respectively, corresponding *trans* configuration, and then the low-field shift of the  $\gamma$ -Ha peak is attributable to the deshielding effect by the  $\beta$ -equatorial phenyl group. These results indicate that the

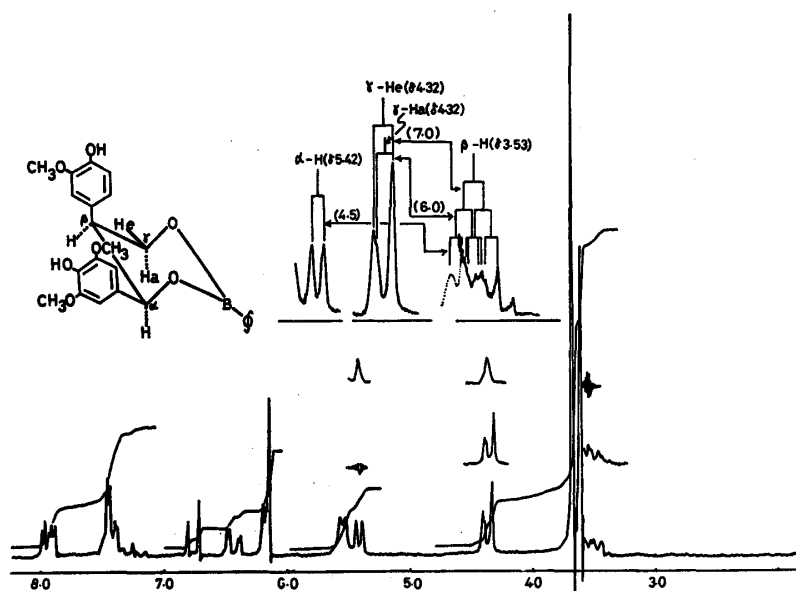


Fig. 32. NMR spectrum of phenylboronate of *erythro*-1,2-diarylpropane-1,3-diol (9a).

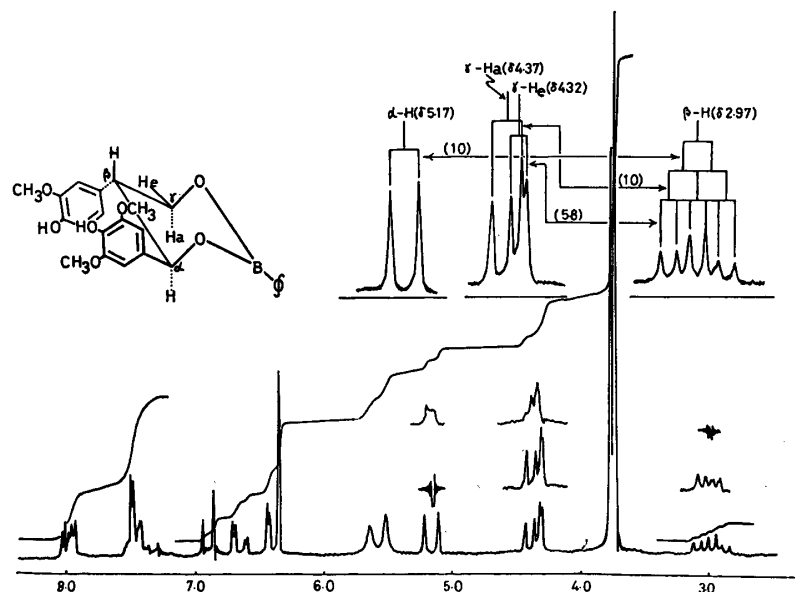


Fig. 33. NMR spectrum of phenylboronate of *threo*-1,2-diarylpropane-1,3-diol (9b).

compound (9b) is the *threo* isomer, and takes the conformation shown in Fig. 33. In contrast, a small coupling constant between  $\alpha$ - and  $\beta$ -protons of the compound (9a), 4.3 cps shown in Fig. 32, corresponds to about  $45^\circ$  of the dihedral angle reflecting axial  $\alpha$ -proton and equatorial  $\beta$ -proton. Consequently, the configuration of the compound (1a) was determined to be *erythro*.

## 2.4 Syntheses of phenylcoumarans<sup>66)</sup>

Phenylcoumaran structure, one of the main constitutional units in lignin, is present in about 14% per C<sub>9</sub>-unit<sup>67)</sup> and has been investigated in relation to lignin reactions such as pulping, chemical utilization and biodegradation of lignin. Besides, the phenylcoumaran derivatives have been isolated from plant extractives<sup>68~74)</sup> recently, and this has promoted interest in the studies of biogenetic differences between optically inactive lignin and optically active lignans. To elucidate such problems, the most suitable phenylcoumaran compounds must be used in each experiment. However, only two phenylcoumaran compounds, dehydrodiconiferyl alcohol and dehydrodiisoeugenol, both obtained by oxidative coupling of coniferyl alcohol and isoeugenol are available, and the general synthetic method of phenylcoumaran is not established yet.

In this Section, the syntheses of dehydrodiconiferyl alcohol and its derivatives, and the first general synthetic method for phenylcoumaran are described.

### 2.4.1 A new general synthetic method of phenylcoumarans

An "irrational" synthetic method<sup>75)</sup> for the phenylcoumarans was reported by E. Schmid *et al.*<sup>76)</sup> who demonstrated that on heating in N,N-diethylaniline at 225°C 2-(1-arylallyl)-phenols are transformed into *trans* 2-aryl-3-methyl coumarans by an



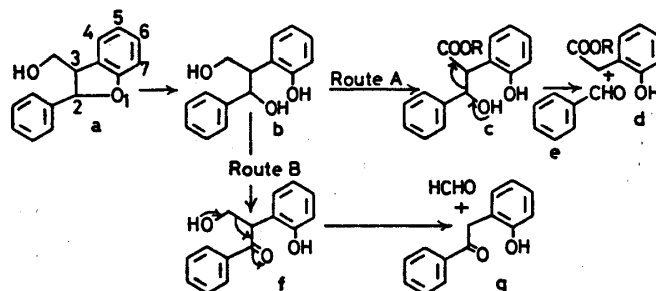


Fig. 34. Synthetic pathway of phenylcoumaran.

abnormal Claisen rearrangement. However, 3-hydroxymethyl coumarans can not be obtained by this method without modification.

Considering a "rational" synthetic method affording 3-hydroxymethyl coumarans, the expected coumaran (a) is thought to be synthetically equivalent to 1,2-diarylpropane-1,3-diol system (b) which can be obtained by two synthetic routes. First, if the terminal hydroxymethyl group is assumed to be equivalent to the ester group, the compound (b) can be converted anti-synthetically into  $\beta$ -hydroxy ester (c) which can be synthesized by an aldol condensation type reaction between *ortho*-hydroxyphenyl acetate derivative (d) and an aldehyde (C) (route A). On the other hand, if the benzylcarbinol group is assumed to be equivalent to the ketone group, the resultant  $\beta$ -hydroxy ketone (f) might be synthesized by an aldol condensation of the deoxybenzoin (g) with formaldehyde (route B). In the present Section, the former possibility *via* a  $\beta$ -hydroxy ester intermediate is discussed.

#### 2.4.2 Synthesis of dehydrodiconiferyl alcohol

The synthetic route of dehydrodiconiferyl alcohol (12) in Fig. 35 is divided into three main steps, *i.e.*, the introduction of a two carbon side chain to C<sub>5</sub>-position of vanillin derivative (compound 5), the formation of the phenylcoumaran ring, which is a key step in the present synthetic method (compound 9), and finally the side chain extension.

The first target molecule (5) is assumed to be obtained by the Claisen rearrangement of *O*-allylvanillin, and subsequent oxidative split-off of the carbon-carbon double bond of 5-allylbenzylvanillin derivative. The oxidation of 5-allylbenzylvanillin acetal gave 5-(2,3-dihydroxypropyl) and 5-formyl vanillin derivatives in low yield even under the mildest condition (OsO<sub>4</sub>/NaIO<sub>4</sub>) and resulted in deprotection of aldehyde at C<sub>1</sub>-position. Therefore, the compound (5) was finally obtained by the following method (Fig. 35).

The compound (1) was prepared by Freudenberg *et al.*<sup>77)</sup> but the intermediate, 5-iodovanillin dimethylacetal, was unstable and decomposed to the starting material without any acid catalyst. Thus, this compound was prepared in over 90% crystallization yield from 5-iodovanillin by benzylation and subsequent acetalization.

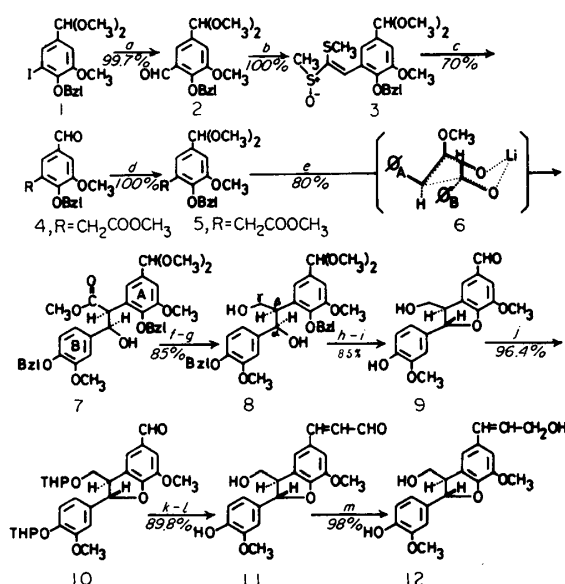


Fig. 35. Synthetic route for dehydrodiconiferyl alcohol (12).

<sup>a</sup> $n$ -BuLi/DMF/Et<sub>2</sub>O/−35°C. <sup>b</sup>FAMSO/NaH/DMF/r.t. <sup>c</sup>HCl/MeOH/5°C. <sup>d</sup>CH(OCH<sub>3</sub>)<sub>3</sub>/ $p$ -TsOH/MeOH/reflux. <sup>e</sup>Lithium diisopropylamide/Benzylvanillin/THF/−70°C. <sup>f</sup>Me<sub>3</sub>SiCl/Et<sub>3</sub>N/THF/r.t. <sup>g</sup>LiAlH<sub>4</sub>/THF/50°C. <sup>h</sup>H<sub>2</sub>/10% Pd-C/MeOH/r.t. <sup>i</sup>BF<sub>3</sub>·Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>/r.t. <sup>j</sup>Dihydropyran/ $p$ -TsOH/CH<sub>2</sub>Cl<sub>2</sub>/0°C. <sup>k</sup> $\Phi_3$ PCH<sub>2</sub>CH(−OCH<sub>2</sub>)<sub>2</sub>Br/ $t$ -BuOK/ $t$ -BuOH-THF/reflux. <sup>l</sup>10% HCl/THF/r.t. <sup>m</sup>NaBH<sub>4</sub>/MeOH/0°C.

The compound (1) was treated with  $n$ -butyl lithium in ether and subsequent  $N,N$ -dimethylformamide to give the aldehyde (2) in the quantitative yield. In this case, when 1,3-dioxolans were used instead of dimethylacetal as protecting group, the cleavage of the acetal occurred. It is assumed that this acetal is fairly unstable because of the electron-donating effect of the benzyloxy group at  $p$ -position and the coordination of lithium cation with the two fixed oxygens of dioxolan having a cyclic structure. It is considered that this coordination acts as a driving force for the cleavage of the acetal, but in the case of dimethylacetal with free rotation, the lithium cation can not coordinate so well. When THF was used as solvent instead of ether, the yield was low with the formation of by-products, because 5-lithio derivative was soluble and unstable in THF. The uses of dimethylacetal as a protecting group and ether as a solvent are therefore essential.

Condensation of the aldehyde (2) with a commercially available methyl methylthiomethyl sulfoxide (FAMSO)<sup>78)</sup> in the presence of sodium hydride in DMF and the subsequent acid-catalyzed methanolysis of the resultant 1-methylsulfinyl-1-methylthioethylenyl derivative (3) led to the formation of the compound (4) in 70% yield. This methanolysis was considerably sensitive to the concentration of acid, and the best yield was obtained under a reaction condition of about 30% hydrogen chloride in methanol at 5°C for 69 hours. The aldehyde (4) was converted to the first target

molecule (5) in the quantitative yield by the acetalization.

The conversion of the compound (5) to the compound (9) is the most significant and interesting step in this synthetic route. Condensation of the compound (5) with benzylvanillin in the presence of lithium diisopropylamide (LDA) in THF at  $-70^{\circ}\text{C}$  afforded the expected  $\beta$ -hydroxy ester (7) in 80% yield. The ester gave colorless crystals from ethyl acetate and *n*-hexane. These crystals were found to be only the *threo* isomer, not a mixture of *erythro* and *threo* isomers generally obtained by aldol condensation reactions. The ratios of *erythro* and *threo* isomers corresponding to the  $\beta$ -hydroxy ester (7) in the syntheses of guaiacylglycerol- $\beta$ -guaiacyl ether and 1,2-diarylpropane-1,3-diol were found to be 3:1<sup>38)</sup> and 1:3<sup>58)</sup>, respectively. Such condensations conceivably proceed via a six-membered transition state, in which the *trans* diequatorial orientation of the bulky functional groups ( $\Phi_A$  and  $\Phi_B$ ) is more favorable than the *cis* orientation for each other because of a steric repulsion in a transition state (6). In the present case, however, only the *trans* diequatorial orientation might be taken place because of the extraordinary steric repulsion with an additional steric hindrance of a benzyloxy group substituted on A-ring, and brought about a highly stereoselective reaction to give only *threo* isomer of  $\beta$ -hydroxy ester (7). This interpretation was supported by NMR of the ester (7); the methylene protons of the benzyl group attached to the B-ring appeared as a singlet at  $\delta 4.97$ , whereas those of A-ring gave an AB type at  $\delta 4.34$  (d,  $J=11$ ) and  $\delta 4.84$  (d,  $J=11$ ), respectively, due to a free rotational hindrance.

It was difficult to obtain the expected diol (8) in high yield by the hydride reduction under various conditions, *e.g.*, reduction with lithium aluminum hydride at  $-50^{\circ}$ ,  $0^{\circ}$  and  $50^{\circ}\text{C}$  and with sodium borohydride in the presence of  $\text{CuCl}_2$  in THF at reflux temperature, *etc.* An  $\alpha$ -deoxy derivative of the diol (8) was always obtained as a main product under these conditions. However, the difficulty was finally solved by trimethylsilylation of the ester (7) with trimethylsilyl chloride and triethyl amine at room temperature and subsequent reduction with lithium aluminum hydride at  $50^{\circ}\text{C}$  afforded the expected diol (8) in 85% yield after purification by silica gel tlc developed with ethyl acetate/*n*-hexane (1:3).

The diol (8), a key intermediate (b) in Fig. 35, thus obtained was unexpectedly easily converted to the phenylcoumaran (9) in 85% yield by catalytic hydrogenation with 10% palladium on carbon and subsequent treatment with catalytic amounts of boron trifluoride etherate in methylene chloride. On addition of boron trifluoride etherate to the hydrogenated compound suspended in methylene chloride, previously dried over alumina, the reaction mixture turned yellow in a moment suggesting instantaneous formation of a quinonemethide-like intermediate in this cyclization.

The phenylcoumaran (9) was unequivocally identified by comparing with those

obtained by the oxidation of dehydrodiconiferyl alcohol ( $\text{OsO}_4/\text{NaIO}_4$  in ether and water, giving about 60% yield) and also by biodegradation of dehydrodiconiferyl alcohol with *Fusarium solani* M-13-179). Since the *trans* configuration of dehydrodiconiferyl alcohol was determined earlier<sup>34)</sup>, the phenylcoumaran (9) must be *trans*.

Finally, the side chain extension of phenylcoumaran (9) to dehydrodiconiferyl alcohol (12) was achieved. In general, malonic acid derivatives have been used as a two-carbon source, but the condensation of a ditetrahydropyranyl ether derivative (10) with these reagents did not proceed smoothly. The Wittig reaction was found to be suitable for this purpose.

The Wittig reaction of the compound (10) with 3.0 mol. equiv. of 1,3-dioxan-2-ylmethyl triphenylphosphonium bromide<sup>80)</sup> in the presence of potassium *t*-butoxide in THF at reflux temperature and subsequent acid hydrolysis afforded the aldehyde (11) in about 90% overall yield. The aldehyde was unequivocally identified comparing with those obtained by oxidative coupling of coniferyl alcohol<sup>56)</sup> and also by biodegradation of dehydrodiconiferyl alcohol<sup>79)</sup>. The aldehyde (11) was finally converted to dehydrodiconiferyl alcohol (12) in quantitative yield by sodium borohydride reduction.

#### 2.4.3 Syntheses of dehydrodiconiferyl alcohol derivatives

To prove that the synthetic method thus established is a general one, the syntheses of various dehydrodiconiferyl alcohol derivatives, which are difficult to obtain in high yield by oxidative couplings of *p*-hydroxycinnamyl alcohols, were tried. When benzylsyringaldehyde was used instead of benzylvanillin at the stage of condensation with the compound (5) in Fig. 35 and the subsequent reactions were followed, the final compound (13), 2-(4-hydroxy-3,5-dimethoxy)phenyl-3-hydroxymethyl-5-(3-hydroxy) propenyl-7-methoxy-coumaran was obtained in almost the same yield, in the respective steps, as in the case of the compound (12). The compound (13) seems to be important in hardwood lignin which is known to be a copolymer of coniferyl and sinapyl alcohols. Its dihydro derivative was actually isolated from hydrolysis products of Mizunara (*Quercus mongolica*) wood<sup>81)</sup>.

When *p*-hydroxybenzaldehyde benzyl ether was used at the stage of the con-

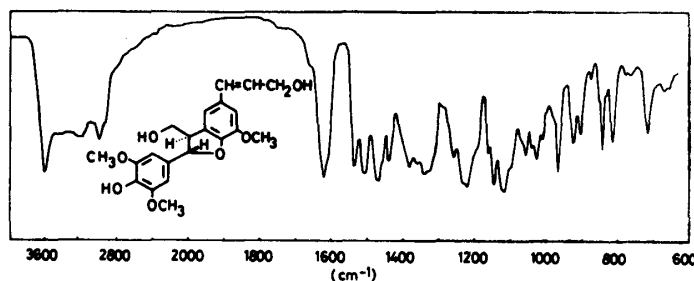


Fig. 36. IR spectrum of a dehydrodiconiferyl alcohol derivative (14).

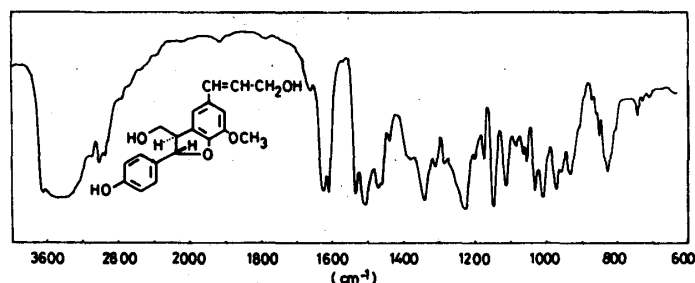


Fig. 37. IR spectrum of a dehydrodiconiferyl alcohol derivative (13).

densation, the phenylcoumaran (14), 2-(*p*-hydroxy) phenyl-3-hydroxymethyl-5-(3-hydroxy)propenyl-7-methoxy coumaran was obtained. The IR spectra of these compounds are shown in Figs. 36 and 37, respectively.

## 2.5 Syntheses of trilignols composed of phenylcoumaran and $\beta$ -O-4 structures<sup>82)</sup>

The general synthetic method of phenylcoumaran was described in previous Section. In this Section, the syntheses of the trilignols composed of phenylcoumaran and  $\beta$ -O-4 structures are described. The trimer is generally difficult to obtain by oxidative couplings of *p*-hydroxycinnamyl alcohols. The syntheses of the compounds (7) and (8) may be important for the following reasons: 1) Demonstration of the applicability of the  $\beta$ -ether synthetic method previously described (Section 2-1) to the syntheses of the trimeric lignin model compound. 2) Acidolysis product due to the phenylcoumaran attached to the  $\beta$ -O-4 component has been isolated<sup>83)</sup> and such a structure is considered to play a fairly important role in lignins. 3) The compounds (7) and (8) are useful for the studies of various lignin reactions. The lignin monomers and dimers exist as bonded units to form lignin polymer, and not as individual entities. Nevertheless, the lignin model compounds used so far are only monomers and dimers. It is reasonable to consider that chemical change arising in one structural unit causes different chemical reactivity in another, as in the case of neighbouring participation of functional group. For example, when a benzylcarbinol group of the structural unit (a) in lignin molecule is oxidized to keto group, the structure (b) which is expressed as a resonance hybrid (c) is formed. Accordingly the ether bond between R'' and oxygen must be more unstable than in the case of (a), and which results in easy decomposition to R''<sup>+</sup> and the structure (d), as shown in Fig. 38. Syringaldehyde has

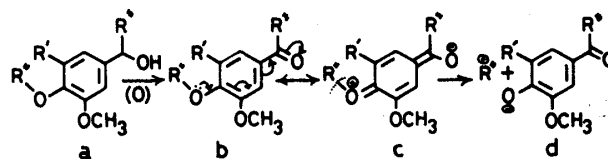


Fig. 38. Effects of neighbouring groups in lignin molecule.

been obtained from 3,4,5-trimethoxybenzaldehyde by selective demethylation with sodium *p*-thiocresolate in 90% yield<sup>84</sup>). For such a experiment, trimeric compounds could be used conveniently.

### 2.5.1 First syntheses of trilignols

The synthetic route for trilignol (8) shown in Fig. 39 is divided into three main steps, the synthesis of  $\alpha$ -phenoxy acetate derivative (1 $\rightarrow$ 4), the synthesis of  $\beta$ -hydroxy ester by an aldol condensation type reaction (4+5 $\rightarrow$ 6) and finally the transformation of functional groups in the side chain (6 $\rightarrow$ 8).

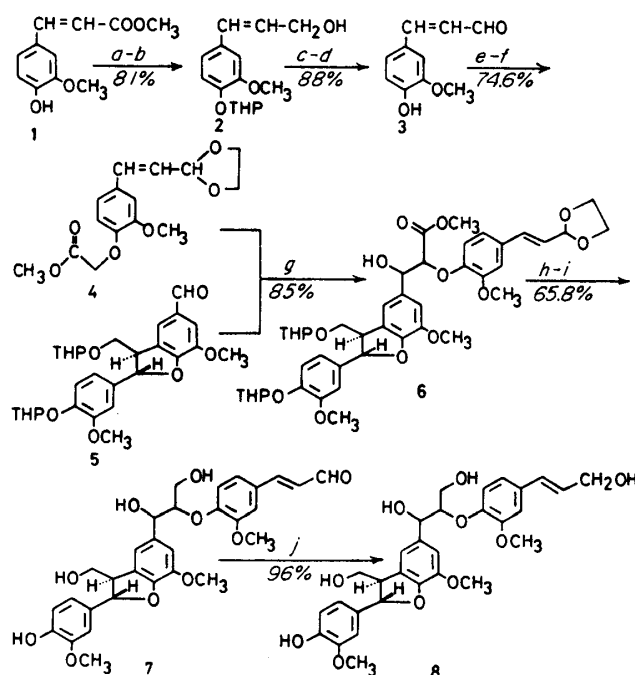


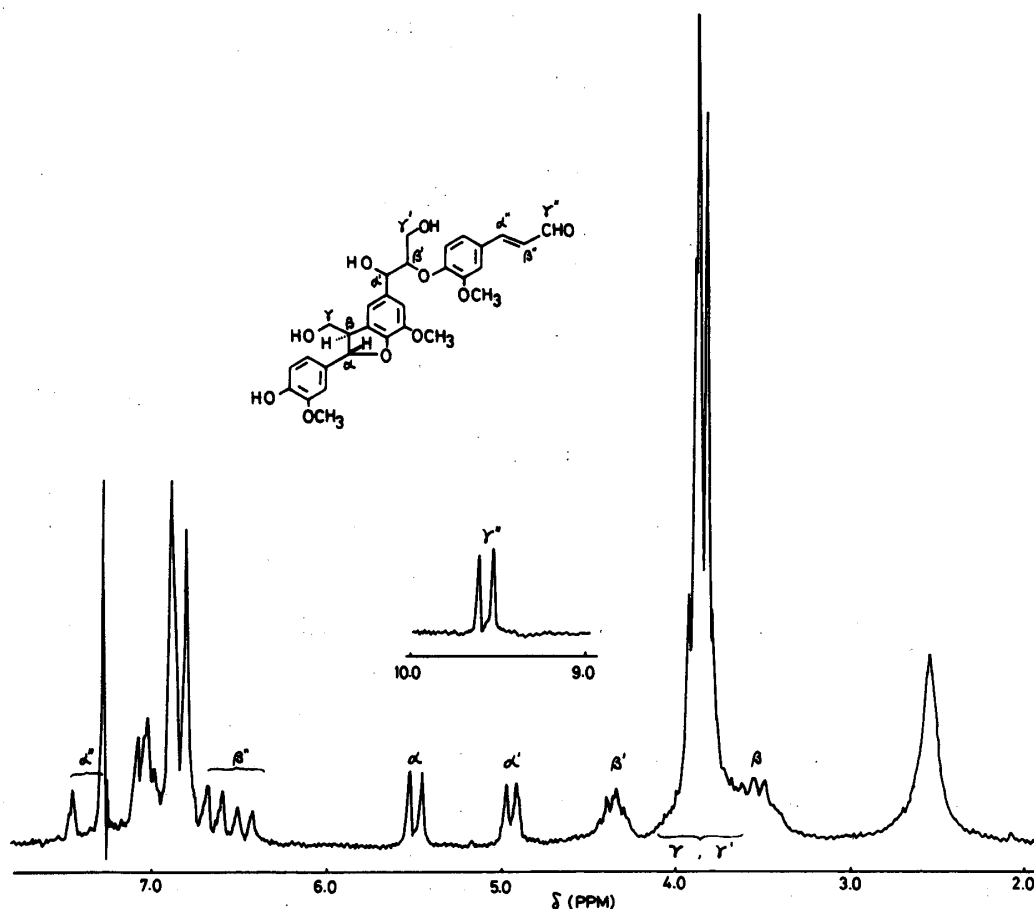
Fig. 39. Synthetic route for trilignols composed of phenylcoumaran and  $\beta$ -O-4 structures.  
<sup>a</sup>Dihydropyran/*p*-TsOH/CH<sub>2</sub>Cl<sub>2</sub>/0°C. <sup>b</sup>LiAlH<sub>4</sub>/THF/−25°C. <sup>c</sup>MnO<sub>2</sub>/CCl<sub>4</sub>/r.t.  
<sup>d</sup>1N-HCl/THF/r.t. <sup>e</sup>ClCH<sub>2</sub>COOCH<sub>3</sub>/K<sub>2</sub>CO<sub>3</sub>/KI/acetone/reflux. <sup>f</sup>Ethylene glycol/*p*-TsOH/benzene/reflux. <sup>g</sup>Lithium diisopropylamide/THF/below −70°C.  
<sup>h</sup>LiAlH<sub>4</sub>/THF/50–60°C. <sup>i</sup>pyridinium *p*-toluene sulfonate/EtOH/50°C. <sup>j</sup>NaBH<sub>4</sub>/MeOH/0°C.

In the first step, coniferyl alcohol was used preliminarily. Coniferyl alcohol was converted to  $\alpha$ -phenoxy acetate derivative with methyl monochloroacetate and base by the usual method, and then the hydroxyl group was protected with tetrahydropyranyl (THP) ether. The subsequent reaction gave reasonable yields except for the final step, the acid-catalyzed hydrolysis of THP ether, which resulted in low yield. In general, coniferyl aldehyde is more stable than coniferyl alcohol under acidic conditions and reduced to the alcohol with sodium borohydride in a high yield. Coniferyl aldehyde was then used as the starting material in the present syntheses.

Although many synthetic methods for coniferyl aldehyde has been reported<sup>85,86</sup>,

the present method is the easiest and gives the best yield. The reason for this is that the oxidation of an allylic alcohol with active  $\text{MnO}_2$ <sup>87)</sup> generally gives an aldehyde in a high yield in non-polar solvent, especially, carbon tetrachloride which can dissolve the THP ether of methyl ferulate. The overall yield from methyl ferulate was about 70%. This synthetic method will be reported in detail elsewhere together with the syntheses of other lignin monomers, *p*-hydroxycinnamaldehyde and sinap aldehyde<sup>88)</sup>.

Coniferyl aldehyde (3) was converted to the  $\alpha$ -phenoxy acetate derivative with methyl monochloroacetate and potassium carbonate and then the aldehyde group was protected with dioxolan to give the compound (4) in 74.6% overall yield. When dimethyl acetal which could be easily obtained by the reaction with methyl orthoformate and catalytic amounts of *p*-toluenesulfonic acid was used preliminarily, the subsequent condensation reaction gave  $\beta$ -hydroxy ester in only 67.5%. It was also shown that dimethyl acetal is more labile than dioxolan and partly decomposed to aldehyde during drying in a desiccator with  $\text{P}_2\text{O}_5$  before use. The dioxolan derivative (4) gave the  $\beta$ -hydroxy ester (6) by condensation with phenylcoumaran (5)<sup>66)</sup> as a



NMR spectrum of trimeric aldehyde (7)

Fig. 40

colorless glass in 85% yield after purification by silica gel tlc developed twice with ethyl acetate/*n*-hexane (1:1). On the NMR spectrum of the  $\beta$ -hydroxy ester (6), respective protons attached to the side chain appear as fairly isolated peaks for each other, nevertheless the  $\beta$ -hydroxy ester (6) has six asymmetric carbons. It is considered based on the discussion of six-membered transition state reported previously<sup>66)</sup> that the *erythro* form is predominant in the configuration between  $\alpha'$  and  $\beta'$ -carbons although no experimental evidence has been obtained.

The  $\beta$ -hydroxy ester (6) was reduced with lithium aluminum hydride to 1,3-propane diol derivative which was then subjected to the hydrolysis of THP ether in ethanol with a tenth equivalent of pyridinium *p*-toluenesulfonate<sup>89)</sup> at 50°C, and the trimeric aldehyde gave a strong magenta coloration with phloroglucinol-HCl reagent gradually turning blue with 2,6-dichloroquinone chloroimide/1*N*-NaOH solution, respectively. The NMR spectrum is shown in Fig. 40. Finally, sodium borohydride reduction of the trimeric aldehyde (7) obtained gave the target molecule, trilignol (8) in 96% yield. The NMR spectrum of this compound is shown in Fig. 41. The

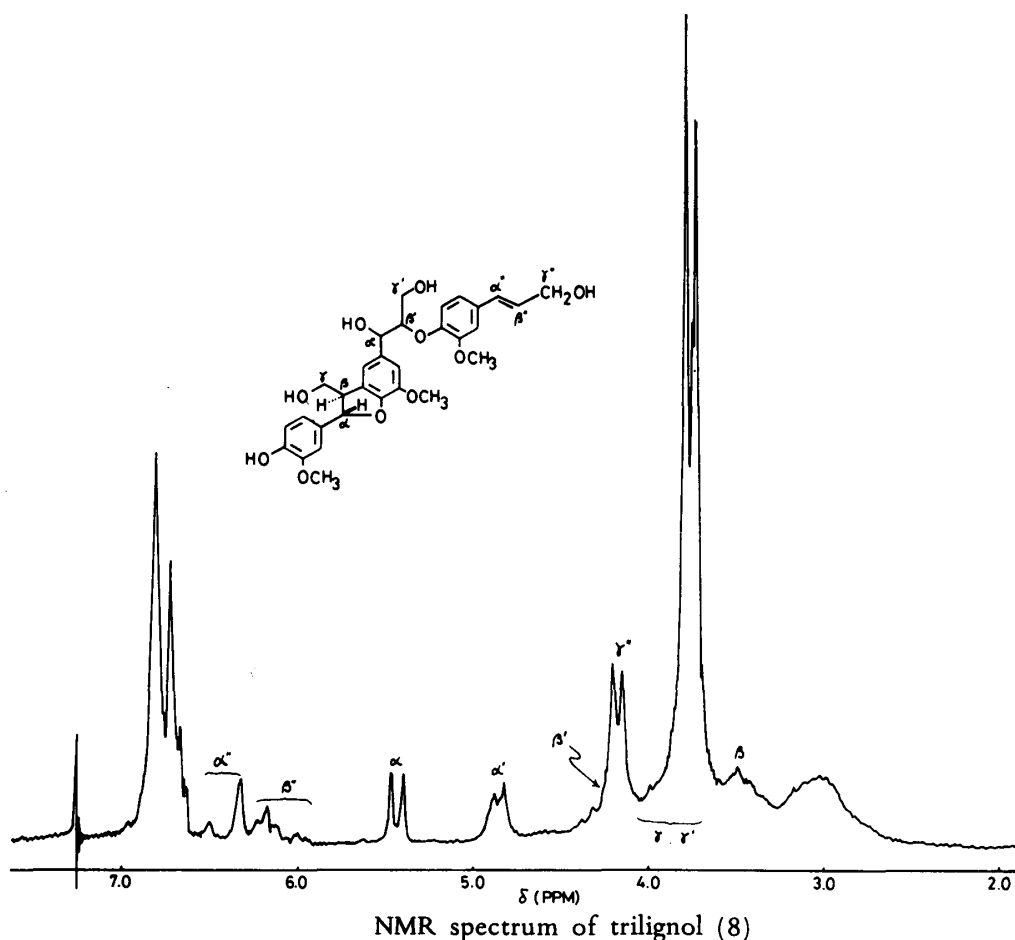


Fig. 41



trilignol (8) was fairly susceptible to air oxidation and gave the trimeric aldehyde (7) in about 20% after standing at room temperature for a month. This observation reasonably explains that freshly cut and thoroughly extracted sections of spruce wood gave a strong coloration for coniferyl alcohol groups, and that the reaction was negative for sections stored in air for six months<sup>90)</sup>.

It was confirmed here that our synthetic method of  $\beta$ -ether lignin model can be applied to the synthesis of trilignol. It is suspected that the other methods hitherto reported may give less satisfactory results in the synthesis of the trilignol (8).

## 2.6 Synthesis of a trilignol composed of phenylcoumaran and $\beta$ -1 structures<sup>91)</sup>

A trilignol (5) composed of phenylcoumaran and  $\beta$ -1 structures has been isolated from the lignin hydrolysis products of Ezomatsu (*Picea Jezoensis*) as an optically inactive compound<sup>92)</sup>. Such a structural unit is considered to play an important role in lignins.

An optically active trilignol (5) was recently isolated<sup>93)</sup> from the heart wood extractives of Japanese larch (*Larix leptolepis*). It is of interest to study of biogenetic difference between optically inactive lignin and optically active lignans.

In this Section, the synthesis of the trilignol (5) is described starting from methyl homovanillate benzyl ether (1) and phenylcoumaran (2).

### 2.6.1 A high yield synthesis of the compound

The synthesis of trilignol (5) may be easily understood based on the synthetic method of 1,2-diarylpropane-1,3-diol described in Section 2-3; the compound might be synthesized from homobenzoic acid derivative (1) and benzaldehyde derivative (2) as shown in Fig. 42. Lithium enolate prepared from methylhomovanillate benzyl ether (1) and lithium diisopropyl amide (LDA) reacted successfully with the phenylcoumaran (2) in THF below  $-70^{\circ}\text{C}$  to give the expected  $\beta$ -hydroxy ester (3) in 87% yield. The compound (3) which contains six asymmetric carbons may occur theoretically as a mixture of thirty two diastereomers. However, the phenylcoumaran ring is fixed *trans* and then the compound (3) is considered to consist of sixteen diastereomers. The  $\beta$ -hydroxy ester (3) gave two spots with Rf-value 0.45 and 0.35, respectively, on a silica gel tlc plate developed with ethyl acetate/*n*-hexane (1:1). Since these two spots become a single spot after acid hydrolysis of THP ethers, the separation of these two compounds is not needed at this stage. The NMR spectrum of the compound (3) is too complicated to be assigned, but the spectrum supported the existence of the phenylcoumaran moiety as shown by acetal protons of alcoholic and phenolic THPs at  $\delta$ 4.00–4.20 (1H, m) and  $\delta$ 5.33 (1H, m), respectively,  $\alpha$ -methine proton of phenylcoumaran at  $\delta$ 5.51 (1H, m) and furthermore, homovanillate moiety by the benzylic methylene and  $\alpha'$ -methine protons at  $\delta$ 4.94–5.17 (3H, m) and aromatic protons of

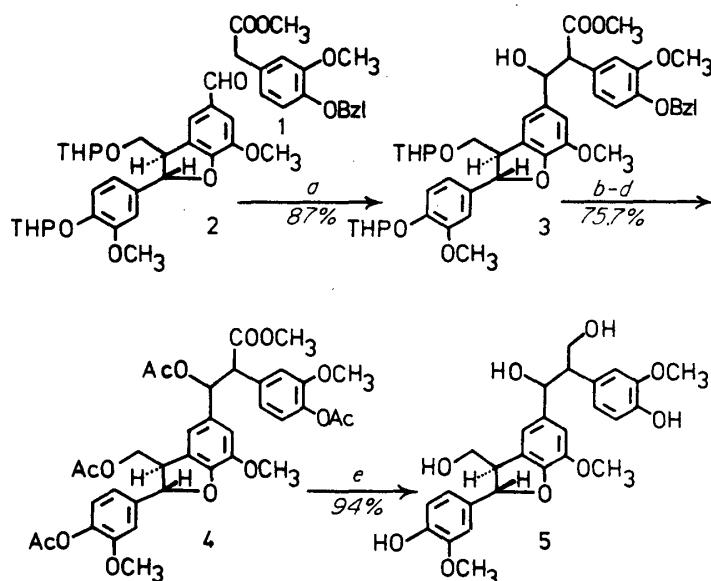


Fig. 42. Synthetic route for a trilignol composed of phenylcoumaran and  $\beta$ -1 structures.

<sup>a</sup>Lithium diisopropylamide/THF/below  $-70^{\circ}\text{C}$ . <sup>b</sup>AcOH-H<sub>2</sub>O (9:1)/ $50^{\circ}\text{C}$  (78.3%). <sup>c</sup>H<sub>2</sub>/10% Pd-C/MeOH/r.t. (97.4%). <sup>d</sup>Ac<sub>2</sub>O/pyridine/EtOAc/ $50^{\circ}\text{C}$  (99.2%). <sup>e</sup>LiAlH<sub>4</sub>/THF/ $50^{\circ}\text{C}$ .

benzyl ether at  $\delta 7.17$ – $7.39$  (5H, m). IR spectrum also showed the existence of the ester group at  $1745\text{ cm}^{-1}$ . These data and the reaction mechanism support the conclusion that the structure exactly corresponds to the expected  $\beta$ -hydroxy ester.

The conversion of the  $\beta$ -hydroxy ester (3) to trilignol (5) might be accomplished by two methods, 1) LAH reduction to diol derivative and the subsequent removal of the protecting groups and 2) the removal of the protecting groups and the subsequent LAH reduction. The former method which has been used for the synthesis of trilignol described in Section 2.5 was examined first. The LAH reduction of the  $\beta$ -hydroxy ester (3) in THF at  $50^{\circ}\text{C}$  gave three spots on a silica gel tlc plate developed with ethyl acetate/*n*-hexane (1:1), in which the lowest spot gave the expected diol derivative in only 40% yield after the purification by tlc. The other two compounds were found to be reduction products from the compound (1) and (2) in 45% and 50% yields, respectively. The formation of these two by-products are due to the retro-aldol condensation of the  $\beta$ -hydroxy ester under the LAH reduction condition. This retro-aldol condensation was avoided to some extent by the trimethylsilylation of the  $\beta$ -hydroxy ester before LAH reduction and the yield was improved to 66.6% by this treatment. A similar result had been also obtained in the synthesis of the dimeric 1,2-diarylpropane-1,3-diols. For the complete elimination of such an unexpected reaction, however, the second method shown in Fig. 42 was carried out.

$\beta$ -Hydroxy ester (3) was dissolved in a solution of acetic acid/H<sub>2</sub>O (9:1) and heated at  $50^{\circ}\text{C}$  for 30 min. under nitrogen. The expected triol derivative which was

obtained in 78.3% yield was subjected to catalytic hydrogenation on 10% palladium carbon to afford the tetraol derivative in 97.6% yield. The acetylation of the tetraol gave the tetraacetyl ester (4) in 99.2% yield. The LAH reduction of the tetraacetyl ester (4) at 50°C in THF gave the expected target molecule, trilignol (5) in 94% yield. The trilignol (5) was slightly hygroscopic and its elementary analysis, corrected for the addition of one mole of water, agreed very closely with the calculated value. The spectroscopic data, UV, IR (Fig. 43) and Mass were identical with those of the lignin hydrolysis product from Ezomatsu (*Picea jezoensis*) isolated by Sano *et al.*<sup>92)</sup> The structure of the isolated trilignol was, therefore, confirmed by this synthetic method except for the stereochemistry of the side chain.

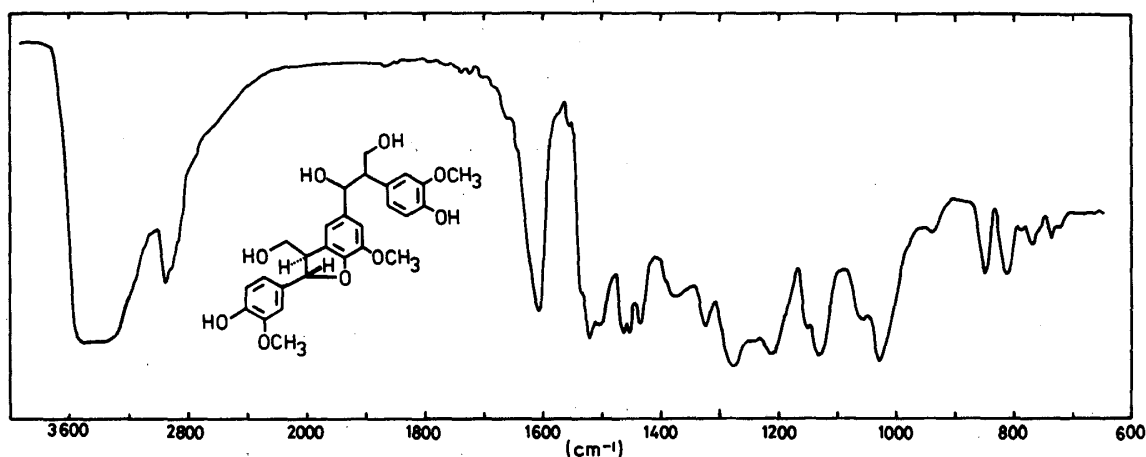


Fig. 43. IR spectrum of a trilignol (5).

NMR analysis of the trilignol (5) is difficult because of overlapping of signals of hydroxyl groups and the protons of the side chains, and then, the NMR spectrum of the acetylated compound was analyzed as shown in Fig. 44. Although  $\beta$ -proton of the compound could not be found because of overlapping with methoxyl groups, two doublet peaks of  $\alpha$ -methine protons at  $\delta$ 5.46 and 5.51 gave a broad triplet by the irradiation at  $\delta$ 3.70 assigned generally as the  $\beta$ -methine proton of phenylcoumaran. On the other hand, two doublet peaks of  $\alpha'$ -methine proton at  $\delta$ 5.90 and 6.03 gave a broad doublet by the irradiation of the  $\beta'$ -proton at  $\delta$ 3.39. It was found that the NMR spectrum was somewhat different from that of the isolated compound. The difference between the synthetic and isolated trilignols seems to be ascribed to the different ratio of the diastereomers. Trilignol containing four asymmetric carbons in which two asymmetric carbons of phenylcoumaran ring are fixed *trans*, is considered to be a mixture of four diastereomers,  $\alpha(S)-\beta(R)-\alpha'(R)-\beta'(R)$ ,  $\alpha(S)-\beta(R)-\alpha'(S)-\beta'(S)$ ,  $\alpha(S)-\beta(R)-\alpha'(S)-\beta'(R)$  and  $\alpha(S)-\beta(R)-\alpha'(R)-\beta'(S)$ , respectively. However, *threo* isomers,  $\alpha(S)-\beta(R)-\alpha'(R)-\beta'(R)$  and  $\alpha(S)-\beta(R)-\alpha'(S)-\beta'(S)$  seems to be more predominant than *erythro* isomers,  $\alpha(S)-\beta(R)-\beta'(S)-\beta'(R)$  and  $\alpha(S)-\beta(R)-\alpha'(R)-\beta'(S)$ .

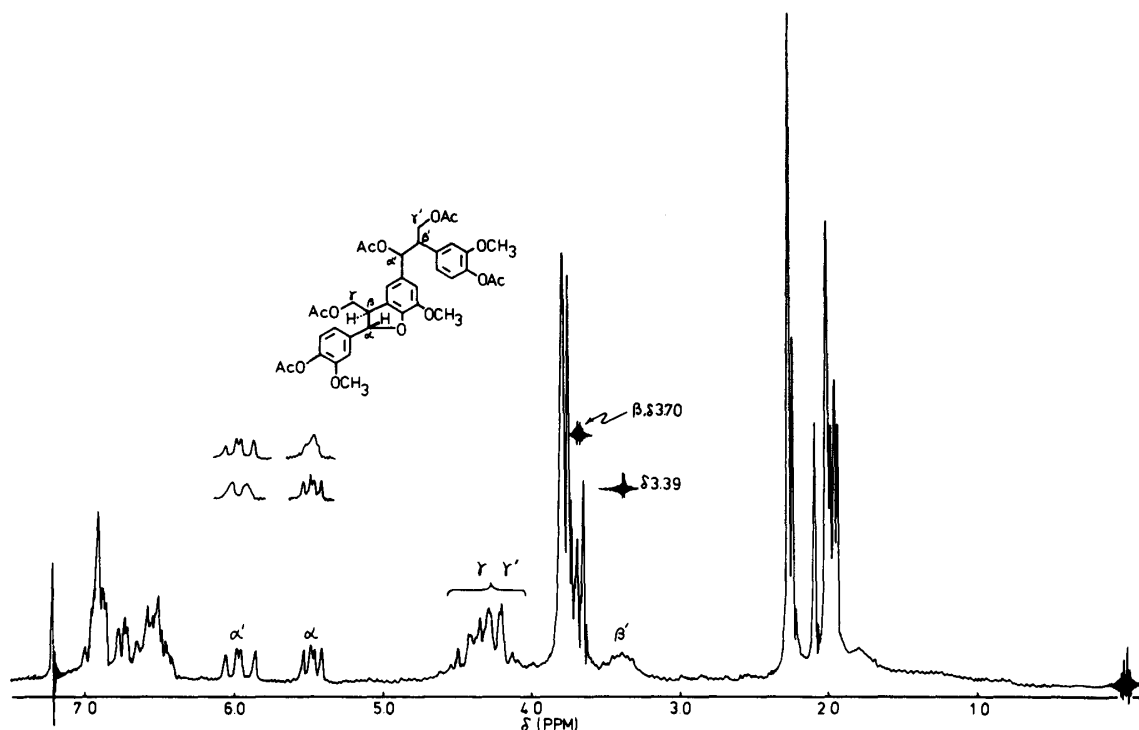


Fig. 44. NMR spectrum of a pentaacetyl trilignol (5).

based on the reaction mechanism *via* the six-membered transition state containing lithium at the step of  $\beta$ -hydroxy ester synthesis. No evidence to support this reasoning has been obtained from this NMR spectrum.

It should be noted that  $\alpha$ - and  $\alpha'$ -methine protons appear as two doublets with almost the same ratio which is reasonably understood to correspond to *threo* isomers rather than *erythro* isomers. To elucidate such a problem, NMR analysis of the phenyl boronate and other six-membered cyclic ketal derivatives of the trilignol (5) is in progress.

### Conclusion

#### *Enzymic dehydrogenation of p-coumaryl alcohol*

*p*-Coumaryl alcohol was dehydrogenated with peroxidase/H<sub>2</sub>O<sub>2</sub> to give four dimeric compounds, *p*-coumarylresinol, dehydrodi-*p*-coumaryl alcohol, *p*-hydroxyphenylglycerol- $\beta$ -*p*-coumaryl ether and 2-(4-hydroxyphenyl)-3-hydroxymethyl-4-( $\alpha$ ,4-dihydroxybenzyl)-tetrahydrofuran (monoepoxylignan). These dimers corresponded to those from coniferyl alcohol except for monoepoxylignan resulted in the *mesoid*  $\beta$ - $\beta'$  coupling which was first identified in the present experiment (Section-1). Furthermore, *p*-hydroxyphenylglycerol was isolated from aqueous solution of dehydrogenation mixture of *p*-coumaryl alcohol after extraction with ethyl acetate, and identified by GC-MS spectrometry compared with the synthetic compound. Both

guaiacylglycerol and syringylglycerol were also isolated from the enzymic dehydrogenation products of the corresponding *p*-hydroxycinnamyl alcohols and identified. These arylglycerols were a mixture of the *threo* and *erythro* isomers and the amount of the former was 1–4 times higher than that of the latter. Arylglycerol was suggested to be formed from the corresponding *p*-hydroxycinnamyl alcohols with peroxidase/ $\text{H}_2\text{O}_2$  and incorporated into arylglycerol- $\beta$ -aryl glycerol ether substructure in lignin polymer during dehydrogenation (Section 1–2).

The direct chemical proof of the configuration of phenylcoumaran ring has been reported here for the first time. The stereochemistry of both rings of dehydrodi-*p*-coumaryl alcohol and dehydrodiconiferyl alcohol, obtained by the dehydrogenation of *p*-coumaryl and coniferyl alcohols, respectively, was investigated chemically as described in Section 1–3. The  $\gamma$ -methyl derivative of dihydrodehydrodiconiferyl alcohol synthesized by the reduction of the double bond in the side chain and also of  $\gamma$ -hydroxymethyl to methyl group was identical with methyl dihydrodehydrodiisoeugenol whose *trans* configuration had been determined. The  $\gamma$ -methyl derivative of dihydrodehydrodi-*p*-coumaryl alcohol was synthesized subsequently by the same method and its *trans* configuration was determined by the comparison of its NMR spectrum with that of methyl dihydrodehydrodiisoeugenol.

Four dilignols isolated and identified in Section 1–1 were analyzed by both gas chromatography and NMR spectrometry, and the ratio of the amounts of main three dilignols was found to be 31( $\beta$ - $\beta'$ ):49( $\beta$ -5):20( $\beta$ -O-4). Furthermore, the following four points were clarified by gas chromatographic analysis; 1) 5–5' dilignol was trace (0.6%). 2) 1,2-di-*p*-hydroxyphenylpropane-1,3-diol which is considered to be formed by  $\beta$ -1 coupling could not be found. 3) the ratio of the *racemoid* and *mesoid* coupling at C- $\beta$  and C- $\beta'$  carbons was about 9.4:1. 4) *p*-hydroxyphenylglycerol- $\beta$ -*p*-coumaryl ether was a mixture of *erythro* and *threo* isomers (1:4.7). These results indicated that coniferyl and *p*-coumaryl alcohols have almost the same reactivity on enzymic dehydrogenation (Section 1–4).

As described in Section 1–2 and 1–4, the water addition to quinonemethide intermediate, which is formed by radical coupling during enzymic dehydrogenation, participates in the formation of arylglycerols and *p*-hydroxyphenylglycerol- $\beta$ -*p*-coumaryl ether. Both compounds occurred as diastereomeric mixture and *threo* isomers were more predominant than *erythro* counterparts. This is different from the expectation that the attack of nucleophile, water in this case, to quinonemethide may occur with the same probability from both sides of planar molecule to afford 1:1 mixture. It was found in Section 1–5 that the rate of the reaction between quinonemethide and various nucleophiles and also the stereochemistry of the products depend on the acidity and the steric factor of the nucleophiles. It was suggested that water

attacks predominantly from the same side with  $\beta$ -hydroxyl or  $\beta$ -phenoxy groups of quinonemethide by forming a hydrogen bonding between water and oxygen atom of  $\beta$ -hydroxyl or  $\beta$ -phenoxy groups, resulting in *threo* isomer.

The present study on the dehydrogenation of *p*-coumaryl alcohol described in Section 1 might be extended to the structural studies of grass lignins and compression wood lignin which contains much more *p*-hydroxyphenyl unit compared with normal wood lignin. The remarkable difference of reactivity between coniferyl and *p*-coumaryl alcohols possibly contributes to condensation *via* C<sub>5</sub>-position of the latter alcohol; it is expected that the prolonged dehydrogenation of *p*-coumaryl alcohol and aging of the DHP in acid condition promotes the formation of C-C linkage *via* C<sub>5</sub>.

#### Syntheses of oligolignols

Considering the main substructure units in lignins, such as  $\beta$ -O-4 (1),  $\beta$ -5 (2),  $\beta$ -1 (3) and  $\beta$ - $\beta'$  (4), the common structural unit in these substructures is thought to be *p*-oxyphenylpropane-1,3-dioxy structure (5) as shown by broad lines in Fig. 45

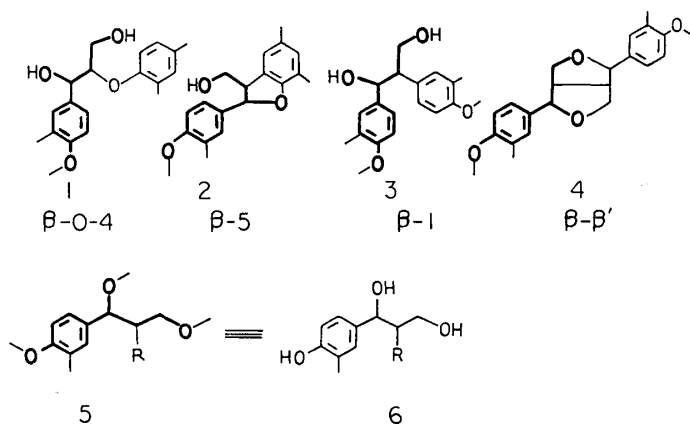


Fig. 45. Common structural unit in lignin substructures.

which is equivalent to *p*-hydroxyphenylpropane-1,3-dihydroxy system (6) from the synthetic point of view. Therefore, the syntheses of lignols and lignin model compounds might be achieved by solving a problem of how successfully this system are synthesized. A "rational" synthesis<sup>75)</sup> to give this system, *p*-hydroxyphenyl-propane-

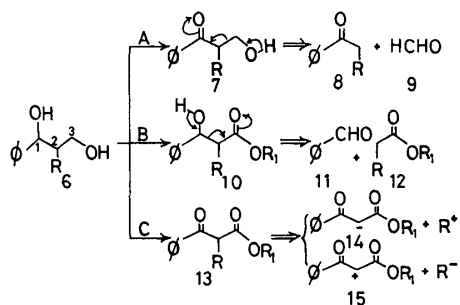


Fig. 46. Synthetic methods for *p*-hydroxyphenylpropane-1,3-diol (6).

1,3-diol (6), would be achieved by three synthetic routes depending on the key intermediates, as shown in Fig. 46. As the benzylcarbinol group is presumed to be equivalent to the keto group, the  $\beta$ -hydroxy ketone (7) might be synthesized by an aldol condensation of the acetophenone derivative (8) and formaldehyde (9) (method A). On the other hand, presuming that the terminal hydroxymethyl group is equivalent to the ester group, this system would be converted into  $\beta$ -hydroxy ester (10) which could be synthesized anti-synthetically by an aldol condensation between acetate (12) and benzaldehyde derivative (11) (method B). The third method C involves  $\beta$ -keto ester (13) as a key intermediate which is derived from the terminal hydroxymethyl and benzyl carbinol groups which are thought to be equivalent to ester and keto groups, respectively. The  $\beta$ -keto ester intermediate (13) could be synthesized from carbanion (14) and  $R^+$ , or carbonium ion (15) and  $R^-$  in carbon-carbon and carbon-oxygen bond formations. The synthetic method of oligolignols

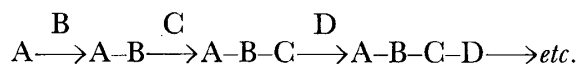
Table 7. Synthetic methods of lignin related compounds reported hitherto and hereafter.

Compounds Methods	$\beta$ -O-4	$\beta$ -5	$\beta$ -1	$\beta$ - $\beta'$
A	O		O	
B	O	O	O	O
C	O			O

- A( $\beta$ -O-4): E. Adler, *et al.*, Sv. Papperstidn., **55**, 245 (1952)  
 E. Adler, *et al.*, Acta Chem. Scand., **9**, 341 (1955)  
 K. Freudenberg, *et al.*, Chem. Ber., **88**, 626 (1955)  
 K. Kratzl, *et al.*, Monatsh., **90**, 771 (1959)  
 H. Nima, Chem. Ber., **100**, 2633 (1967)  
 G.E. Miksche, Acta Chem. Scand., **27**, 1355 (1973)  
 S. Hosoya, *et al.*, Mokuzai Gakkaishi, **26**, 118 (1980)
- B( $\beta$ -O-4): K. Freudenberg, *et al.*, Ann., **584**, 40 (1953)  
 K. Lundquist, *et al.*, Acta Chem. Scand., **29**, 726 (1975)  
 F. Nakatsubo, *et al.*, Holzforschung, **29**, 165 (1975)  
 K. Lundquist, *et al.*, Acta Chem. Scand., **31**, 725 (1977)  
 F. Nakatsubo, *et al.*, Wood Research, **66**, 23 (1980)  
 F. Nakatsubo, *et al.*, Mokuzai Gakkaishi, **26**, 31 (1980)  
 T. Katayama, *et al.*, *ibid*, **27** (1981)  
 H. Namba, *et al.*, *ibid*, **26** (1980)  
 Y. Kamaya, *et al.*, *ibid*, **26** (1980)
- C( $\beta$ -O-4): I.A. Pearl, *et al.*, J. Org. Chem., **27**, 2111 (1962)  
 G.E. Miksche, *et al.*, Acta Chem. Scand., **20**, 1038 (1966)
- B( $\beta$ -5): F. Nakatsubo, *et al.*, Mokuzai Gakkaishi, **25**, 735 (1979)
- A( $\beta$ -1): K. Lundquist, *et al.*, Tetrahedron Letters, **25**, 2131 (1965)
- B( $\beta$ -1): F. Nakatsubo, *et al.*, Holzforschung, **29**, 193 (1975)  
 F. Nakatsubo, *et al.*, Mokuzai Gakkaishi, **26**, 107 (1980)
- B( $\beta$ - $\beta'$ ): H. Fujimoto, *et al.*, *ibid*, **27** (1981)
- C( $\beta$ - $\beta'$ ): K. Kratzl, *et al.*, Monatsh., **94**, 434 (1963)

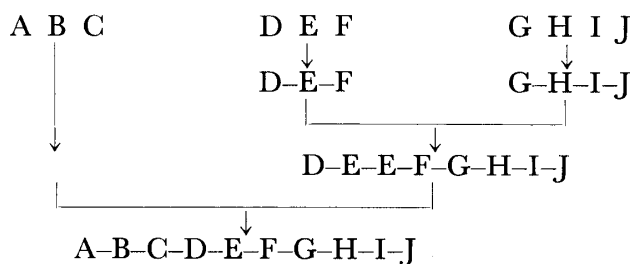
and lignin model compounds reported hitherto and hereafter are summarized on Table 7 based on this basic idea except for the syntheses of 1,2-diarylpropane-1,3-diols via benzylox rearrangement of chalcone reported by P. Kristersson *et al.*<sup>94)</sup>. The circles on the table indicate the methods reported already. For example, A( $\beta$ -O-4) shows the synthetic method of guaiacylglycerol- $\beta$ -guaiacyl ether by E. Adler *et al.* and K. Kratzl *et al.*, and B( $\beta$ -O-4) shows the convergent synthetic method described in this paper, and C( $\beta$ -O-4) shows the method by I. A. Pearl *et al.* and G. E. Miksche *et al.* Of these three methods A, B and C, method B seems to be especially attractive because of the convergent synthesis involving direct  $\alpha,\beta$ -bond formation of lignin substructures.

In general, two major synthetic ways are conceivable for multiatomic molecules<sup>95)</sup>: In the "linear" method the molecule comprised of the units A, B, C, D.....M is synthesized commencing with unit A, adding B, subsequently adding C to the resultant A-B, and so on:



Since organic reactions scarcely give a 100% yield it is clear that with the linear method a long sequence of reactions will require a large amount of starting material A. Adding a similar amount of unit B may increase the yield of A-B but soon the amount of A-B-C-D becomes larger compared to the added units E, F, G and the yield may decrease alarmingly resulting in very little end product.

For this reason the second "convergent" method is generally preferable: the units A-B-C, D-E-F, G-H-I-J which are separately built up by the linear method would be linked together subsequently. This strategy enables workers to keep reasonable amounts of the units A-B-C and D-E-F separately: when approximately equal weights of the both units are used the resulting A-B-C-D-E-F is probably obtained in good yield. Another advantage of the convergent method is that even if a batch of A-B-C is inadvertently lost it does not bring a catastrophic result because these subunits will be obtained by the comparative short steps different from the case of that the material A-.....J becomes increasingly precious as single units in the linear method. In general, for short syntheses the linear method may be used whereas for long syntheses a combination of the linear and convergent methods may be preferable.

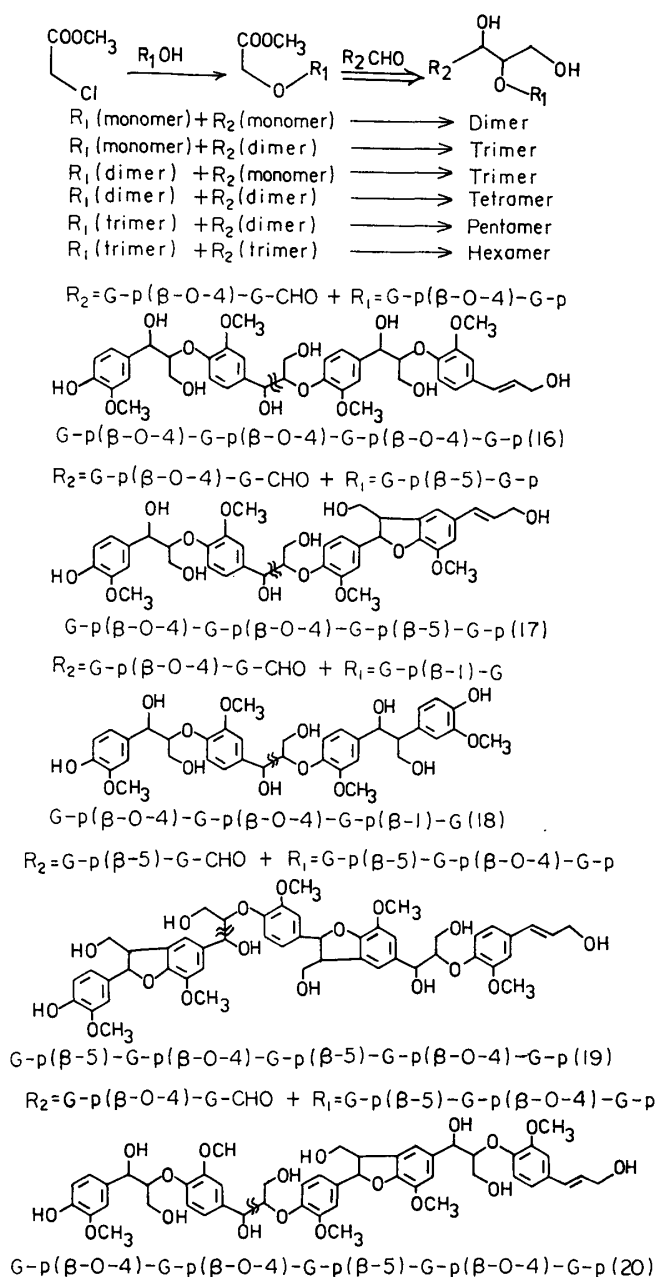




Consequently, although the "linear" method A and C in Fig. 46 could be used for the syntheses of comparatively smaller molecules such as monomeric and dimeric compounds, the syntheses of other higher lignols, trimeric and tetrameric compounds *etc.* would be achieved only by the convergent method B which make it possible the synthesis of any kind of oligolignols.

In Section 2, based on the above discussion the generality of this convergent synthetic method B was confirmed experimentally. In Section 2-1, the high yield convergent synthesis of guaiacylglycerol- $\beta$ -guaiacyl ether which has been used as the most popular model for the  $\beta$ -O-4 substructure in lignins was achieved *via* five steps involving the key condensation between ethyl 2-methoxyphenoxy acetate and benzylvanillin in the presence of lithium diisopropyl amide. The overall yield of the expected compound from benzylvanillin was about 72% which is the best yield recorded so far. This basic idea was further applied for the syntheses of dilignols, guaiacylglycerol- $\beta$ -coniferyl and  $\beta$ -coniferyl aldehyde ethers, which are difficult to obtain by the dehydrogenation of coniferyl alcohol, and the novel high yield syntheses of these compounds were accomplished as described in Section 2-2. In Section 2-3, a new general synthesis involving  $\beta$ -hydroxy ester key intermediate of 1,2-diarylpropane-1,3-diol containing different aryl groups was established in high yield and their configurations were determined by NMR analysis of their phenyl boronate derived from the 1,3-propanediol system of the lignols. The first synthetic method of dehydrodiconiferyl alcohol is described in Section 2-4 and the method was applied successfully for the syntheses of different types of phenylcoumarans which have been isolated from the lignin degradation products in low yield but rarely from the dehydrogenation of *p*-hydroxycinnamyl alcohols. The usefulness and validity of the above synthetic methodology was further proved by its application for the syntheses of trilignols composed of phenylcoumaran,  $\beta$ -O-4 and  $\beta$ -1 stbstructures as described in Section 2-5 and 2-6, respectively.

Arylglycerol- $\beta$ -aryl ether ( $\beta$ -O-4) structure is the most important substructure in lignins, and 30-50% or more of the phenylpropane units have been found as this structure. It is interesting that the present convergent synthetic method could be applied for the syntheses of other higher oligolignols by the  $\beta$ -O-4 bond formation between oligomers which have been synthesized so far: The principle of the present synthetic method is the direct  $\alpha,\beta$ -bond formation by the use of commercially available methyl monochloroacetate, "joint reagent", as two-carbon source between a phenol ( $R_1$ -OH) and a benzaldehyde derivative ( $R_2$ -CHO) as follow:



If a dimeric benzaldehyde derivative,  $\text{G-p}(\beta\text{-O-4})\text{-G-CHO}$  and a dimeric phenol  $\text{G-p}(\beta\text{-O-4})\text{-G-p}$  synthesized in Section 2-2 were used as the starting materials, finally the tetrameric lignol (16) composed of only  $\beta\text{-O-4}$  linkage would be obtained as end product. Similarly if a dimeric benzaldehyde,  $\text{G-p}(\beta\text{-5})\text{-G-CHO}$  and a trimeric phenol,  $\text{G-p}(\beta\text{-5})\text{-G-p}(\beta\text{-O-4})\text{-G-p}$  synthesized in Section 2-4 and 2-5, respectively were used, a pentameric lignol (19) would be prepared and so on. Thus, the convergent synthetic method B of oligolignols involving  $\beta$ -hydroxy ester key intermediate prepared by the use of lithium diisopropyl amide has satisfactorily established, and the method

could be applied successfully for the syntheses of higher oligolignols, tetramers, pentamers and hexamers *etc.*, only in consideration of protecting groups. It seems that the present synthetic strategy will become increasingly important for the future of lignin chemistry toward the complete utilization of lignins, fourth period in lignin history after the end of third period in 1970.

### Acknowledgement

The author wishes to express his sincerest thanks to Professor Dr. Takayoshi Higuchi, Research Section of Lignin Chemistry, Wood Research Institute, Kyoto University, for his kindest guidance and encouragement throughout the course of this work.

The author is deeply grateful to Professor Dr. Tokuo Yokota, Department of Wood Science and Technology, Faculty of Agriculture, Kyoto University and Professor Dr. Yuzo Inouye, The Institute for Chemical Research, Kyoto University, for their valuable suggestions and a critical reading of this manuscript. Thanks are also due to all members of Research Section of Lignin Chemistry for their kind help and discussion.

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